Non-communicable respiratory disease in low- and middle-income countries

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1. INTRODUCTION

Non communicable diseases (NCDs) are a major cause of morbidity and mortality worldwide, accounting for approximately 70% of global deaths.[1] The United Nations' Sustainable Development Goals (SDG) Target 3.4 aims to reduce the risk of premature mortality from NCDs by one third by 2030. Chronic respiratory diseases (CRDs) are common and frequently neglected NCDs that span the life course, affecting children, adolescents and adults. They are associated with high levels of morbidity and risk of mortality due to frequent symptoms, activity limitation, and intermittent exacerbations or 'attacks' requiring acute care. CRDs disproportionately affect the poor and those in low- and middle-income countries (LMICs) where there often few resources available to prevent or manage them.[2]

This review focuses on asthma, COPD, bronchiectasis and post-TB lung disease in LMICs. We discuss the early life origins of many of these conditions, difficulties in diagnosis and management in LMICs, research priorities, broader health system challenges, and strategies for research and clinical capability strengthening for CRD care in LMICs. We propose pathways to solutions that would contribute to achieving the SDGs for health including reducing premature mortality from NCDs and helping to achieve Universal Health Coverage (UHC).

2. EARLY LIFE ORIGINS OF CHRONIC RESPIRATORY DISEASE

Evidence from high income countries (HICs) indicates that the *in utero* environment is crucial for lung development, and that lung function at pre-school age predicts lung function in early adulthood and beyond, into at least the seventh decade of life.[3 4] Early data from the Drakenstein child health study in South Africa – one of the first birth cohorts in the sub-Saharan African setting – confirm that the same is true in LMICs, with lung function tracking from birth through to the preschool years.[5] Common to both settings, but more prevalent and severe in LMICs, are *in utero* and early childhood exposures related to maternal illness and social deprivation, environmental exposures including indoor and outdoor pollution, malnutrition, and a high burden of respiratory and systemic infections. All of these may inhibit lung development such that individuals fail to reach an optimal peak in early adulthood, and increase the risk of CRDs later in life. The high burden of detrimental early life exposures in LMICs may explain the lower lung volumes observed amongst asymptomatic non-smoking adults in many sub-Saharan African settings, compared to age- and height-matched adults in HICs.[6] This finding in LMICs is of concern because reduced forced expiratory volumes in 1-second (FEV_1) and forced vital capacity (FVC) in adulthood have been associated with cardiovascular and metabolic morbidity, as well as differences in mortality both within and between populations.[4 7 8]

In-utero exposures

Tobacco and air pollution: In utero exposure to nicotine is thought to alter lung structure and function, and immune responses in the developing foetus. Analysis of exposure and outcome data for 675 infant and mother pairs within the Drakenstein cohort found that one third of mothers smoked during pregnancy, with lower tidal volumes and higher lung clearance indices at age 6 weeks (implying impaired lung and airway development) observed in infants of smoking women compared with non-smoking women.[9] Similar outcomes have been seen in relation to other forms of air pollution exposure.[10]

Social deprivation: Maternal stress, adverse living conditions, and intimate partner and neighbourhood violence are all too common in LMICs.[11] Maternal psychological distress is associated with measures of neonatal health including weight for age and head circumference,[11] but has not been shown to directly predict child lung function. Maternal alcohol exposure during pregnancy adversely impacts lung function at 6-weeks, but this effect is no longer seen by one-year.[5 9]

HIV infection: Maternal HIV prevalence remains high in many LMICs but the introduction of 'test and treat' approaches to antiretroviral treatment with programmes to prevent maternal to child transmission have dramatically decreased rates of perinatal infection. Whilst HIV-exposed but

uninfected infants may have reduced early lung function, by age two years residual impairment is seen only in those children whose mothers had poorly controlled HIV disease during pregnancy.[12]

Childhood exposures

Acute lower respiratory infection: Early childhood bacterial and viral infections are common in LMICs and are both a consequence of poor general health and associated with ongoing respiratory illness. Respiratory syncytial virus (RSV), rhinovirus (RV), adenovirus and Influenza A are amongst the most common pathogens detected in children with acute respiratory illnesses in LMICs.[13 14] Data from HICs indicate that wheezing illnesses associated with RV and RSV in early life are strong predictors of childhood asthma by 6-years of age,[15] whilst lower respiratory tract infection (LRTI) associated with adenovirus has been associated with obliterative bronchiolitis/bronchiectasis in sub-Saharan African countries. Pneumonia (incidence ~0.2-0.3 episodes/child year) is a major cause of mortality in children,[16] and LRTIs in early childhood are an independent risk factor for reduced lung function by 1-year.[9] It remains unclear whether such early life respiratory infections are manifestations of predisposition to chronic lung disease or independent causes of later disease.

Pulmonary tuberculosis: Children <15 years account for 11% of incident TB cases globally,[17] and paediatricians in LMICs routinely report seeing a high burden of post-TB sequelae including bronchial stenosis, bronchiectasis, and lung destruction.

Chronic HIV infection: Large numbers of children previously infected with vertically-acquired HIV are now growing into adolescence.[18] These long-term survivors experience a high burden of CRDs including bronchiectasis, and bronchiolitis obliterans.[18 19]

Malnutrition: LMICs increasingly face a dual burden of maternal and childhood malnutrition, which results in foetal growth restriction, stunting, wasting, and isolated nutrient deficiencies, but also children who are overweight or obese.[20] Limited data are available suggesting in utero and early childhood starvation has adverse effects on lung development that persist into adult life. Obesity is also thought to cause long term airway disease. [21]

Environmental exposures: The relationship between early childhood biomass fuel exposure and lung development remains unclear: delayed introduction of clean burning stoves into Guatemalan households (at child age 18-57-months vs <6m) was associated with lower, but not statistically significant, rates of lung growth,[22] 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.[23]

Meeting the challenge

Most predictors of poor lung development in utero and early childhood are amenable to public health interventions, particularly interventions on smoking cessation, alcohol reduction and improved nutrition in women of childbearing age. These interventions should include both health promotion and political action such as taxation and regulation of advertising through effective legislation. The latter may be particularly relevant in the context of rapid development and increasing marketing and interference by tobacco, alcohol and food and beverage companies in LMICs, with limited national regulatory frameworks.[2] Programmes that support HIV infected mothers to prevent perinatal transmission, and the provision of early childhood HIV testing must be maintained. Maternal education about childhood nutrition and vaccination is important. Lastly, the socioeconomic environment is a key determinant of respiratory and general health. Efforts to alleviate poverty among mothers and children will be paramount for improving respiratory and other childhood outcomes.

ASTHMA

Asthma is the most common chronic respiratory disease globally, affecting more than 350 million people in 2015,[24] with extremely high rates of asthma-related deaths in LMICs compared with HICs.

This is likely related to lack of access and underutilisation of effective treatments for prevention of acute attacks, in particular inhaled corticosteroids.

Diagnosis

The Global Initiative for Asthma (GINA) indicates 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.[25] However, access to these tools remains limited in LMICs, such that diagnostic capacity is severely constrained.[26]

Management

Inhaled corticosteroids (ICS) improve the control of asthma symptoms, and prevent exacerbations and deaths in people with asthma.[27] However, ICS are frequently underutilised by people with asthma in LMICs owing to their cost or non-availability. Instead there is over-reliance on relievers such as inhaled bronchodilators, oral preparations of salbutamol and theophylline.[28 29] Long-term follow-up with up-titration of medication for symptom control remains limited, with 52-76% loss to follow-up seen within 1-year in pilot projects in China, Benin and Sudan.[29 28] As-required use of inhalers combining ICS with the rapid-onset bronchodilator formoterol is now recommended by the Global Initiative for Asthma (GINA) for adolescents and adults at treatment steps 1 and 2.[25 31] This is based on recent large clinical trials which show 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, with a much lower dose of ICS but no clinically important difference in symptom control.[32-35] Likewise, in moderate-severe asthma, maintenance and reliever therapy with combination ICS-formoterol reduces severe exacerbations compared with conventional ICS-LABA therapy with SABA reliever. In mild asthma, if combined ICS-rapid-onset-bronchodilator preparations are not available or affordable in LMICs, ICS should be used whenever a SABA is taken.

Meeting the challenge

Global guidelines for asthma care in LMICs are available and must be adapted and adopted for national use in LMICs, with guidance for standardised decentralised care by a variety of levels of health care workers; doctors, nurses and health extension. Implementation requires health worker training to recognise clinical presentations of asthma (syndromic diagnosis), and improved access to diagnostic tools (peak flow meters and spirometry), and quality-assured essential asthma medicines. The inclusion of budesonide-formoterol on the WHO Essential Medicines list that may be used as controller and reliver, may facilitate this if made more widely available.[36] Education of both patients and providers will be required to ensure appropriate prescription and use of inhalers, with emphasis on the use of ICS and training in inhaler technique. In the acute setting, use of pressurized metered dose inhalers (pMDI) with or without spacers, which are as effective as nebulisers, may demonstrate the effectiveness of inhalers for symptom relief and encourage ongoing use. Health services with capacity for follow-up for patients with this chronic disease is rare in LMIC, but essential for preventing over-reliance on emergency services, and improving long-term symptom control and maintenance of productive lives for patients.

COPD

The global burden of COPD is heterogeneous, with widespread variability in the prevalence, causes, clinical presentation and mortality reported between and within LMICs. This is compounded by controversy over how to define abnormal spirometry results (e.g. whether percent predicted or lower limit of normal (LLN) boundaries should be used to identify abnormal results, and which reference ranges to use for standardisation of measurements) and whether to consider all patients with fixed airflow limitation as having COPD.[6] Community-based data indicate that the prevalence of airway obstruction is between 6–20% in Latin America,[37-39] and 5–24% in SSA.[40-43] 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 disability adjusted life years (DALYs).[24] Tobacco smoking remains the dominant risk factor for airway obstruction in LMICs, but between a third to a fifth of cases are seen in never smokers in these settings.[44-47]

Diagnosis

High rates of underdiagnosis and misdiagnosis have been observed globally: ~~in the PLATINO study these were 89% and 77%,[48] and data from a primary care population in Latin America indicate rates of 77% and 30.4%.~~ [49] Combined analysis of data from national and international COPD surveys indicates that over 80% of COPD cases identified on spirometry remain undiagnosed within routine clinical care.[50] Perhaps unsurprisingly those with mild disease and without a history of exacerbations or admissions are less likely to have a diagnosis, but race, educational status, and lack of contact with health services also emerge as risk factors for underdiagnosis, suggesting broader socioeconomic determinants also.[49 50] As noted above, global access to spirometry is limited, and given this is the crucial diagnostic test for COPD, this is likely a key constraint.

Management

Gold 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 (SABA and long-acting ß$_2$ agonists (LABA), long-acting muscarinic antagonists (LAMA), and ICS) according to the severity of disease. These interventions are largely under-utilised in LMICs. In Latin America, population based surveys indicate that only half of smokers had physician counselling, a quarter received any respiratory medication, and influenza vaccination was scarce.[51 52] Results from the PUMA study showed that in primary care, the most widely used inhaled therapy was short-acting bronchodilator with long-acting bronchodilators and ICS relatively less used.[53] There are no clinical trials that have investigated the appropriate pharmacotherapy for non-smoker COPD in LMICs, which may differ from that required by those with smoking-related COPD.

Meeting the challenge

Many of the challenges around the diagnosis and management of COPD are similar to those outlined for asthma, including better access to spirometry and inhaled therapies (long-acting bronchodilators), education for both patients and health care providers, access to long term follow-up care, and use of approved standardized guidelines. Lack of access to spirometry has been shown to be the strongest predictor for an incorrect diagnosis of COPD in LMICs.[55] Broader access to cost-effective non-pharmacological interventions including smoking cessation and pulmonary rehabilitation are also needed. Controversies about the interpretation of spirometry in LMICs must be resolved – classification systems must be validated against long-term patient outcomes, in order to ensure that treatment efforts are focused on groups with genuine pathology who are most likely to benefit from active management. Lastly, in the presence of limited resources, a better understanding of how to prevent, diagnose and treat COPD in LMICs is paramount.[57] Smoking remains the key driver of COPD globally, and lessons learnt in HICs about public health and policy approaches to regulation must be urgently translated across to LMICs. However, more data on the risks, nature, outcomes and management of non-smoking related airway obstruction in these settings is also needed.

BRONCHIECTASIS

The reported population prevalence of non-cystic fibrosis bronchiectasis in HICs has increased in recent years to 566/100,000,[58] with disease prevalence and severity associated with older-age and female-gender. Evidence on the epidemiology of bronchiectasis in LMICs is however lacking,[59] perhaps because bronchiectasis is defined by the presence of abnormal dilatation and distortion of airways seen on computerised-tomography (CT) imaging which is a technology not widely available in resource

poor settings. However, it appears that the prevalence, aetiology, and risk for bronchiectasis may be markedly different in LMICs, with more post-infectious disease, a higher burden of more severe disease in younger adults, and differences in colonising / infecting microbiology.[58 60 61]

Diagnosis

Diagnosis of bronchiectasis in LMICs remains challenging. The clinical presentation is with chronic cough and sputum production in adults, and 'failure to thrive' in children with chronic respiratory symptoms and recurrent infections. However, 'gold standard' diagnosis of bronchiectasis requires CT imaging, but its presence may be surmised when chest X-ray features are extensive; ring shadows, fluid filled saccules and tramlining. To our knowledge there are no guidelines for syndromic diagnosis of bronchiectasis in LMICs, nor evidence of the sensitivity / specificity of chest x-ray changes alone.

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.[62] These individualised approaches are not widely available in LMICs, and there is need for developing feasible and scalable programmatic approaches and treatment guidelines for bronchiectasis in LMICs. [58] In many LMICs this may form part of the TB programme, which may be the commonest cause of bronchiectasis. Vigilance for recurrences of active pulmonary TB must be maintained.

Meeting the challenge

Education of health workers about bronchiectasis as a cause of chronic cough is required. Use of 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. More affordable diagnostic approaches suitable for LMICs should be developed, although CT imaging is becoming more widely available. Important research questions include understanding the microbiology of bronchiectasis in LMICs in both children and adults to inform population-level antibiotic recommendations. More epidemiological data on the burden and risk factors for bronchiectasis in LMICs are needed, and would be facilitated by inclusion of LMIC data in bronchiectasis registries; this would also further facilitate the inclusion of research priorities for bronchiectasis in LMICs in international consensus documents.

POST TB LUNG DISEASE (PTLD)

Pulmonary tuberculosis (pTB) survivors, estimated at 58 million in this century alone,[17] have two-to-four-fold odds of persistently abnormal spirometry in adulthood (airway obstruction and low FVC patterns) compared to TB-naïve groups, with bronchiectasis, parenchymal cavitation and destruction, and fibrotic change seen on imaging.[63-66] Mortality in adult survivors of TB is almost three-times that in healthy controls and the excess is frequently due to non-respiratory causes[67]; however, the direct association between PTLD and mortality remains unclear. Of the 10 million annual cases of incident pTB, over 1 million occur in children,[17] yet very little is known about the long-term impact on PTLD in this population.

Diagnosis

Post TB lung diseases are heterogenous and include both structural and physiological lung abnormalities. Diagnosis can be made from spirometry or chest x-ray imaging, but these tests are not routinely performed at successful TB treatment completion. Thus, the majority of patients with PTLD are therefore discharged without ongoing care. Persons who have previously been treated for pTB are at increased risk of recurrence, whether re-activation or re-infection. TB diagnostics may have limited specificity in this group,[68-70] and those with PTLD have a high risk of unnecessary retreatment, with its

attendant risk of side-adverse.[71] and there are no guidelines available for the diagnosis of underlying PTLD or active management to prevent ongoing clinical decline.

Management

There are no evidence-based guidelines for the diagnosis and management of PTLD,[72] or on the rational use of TB diagnostics to identify recurrent disease in this group. TB treatment guidelines pay little attention on long-term morbidity, and health systems remain poorly equipped to provide ongoing care.[73] Current guidance for PTLD management in LMICs is based on approaches developed and used for COPD and bronchiectasis; education about avoiding cannabis and smoking which are common co-exposures in the TB population, remaining physically active, using airway clearance tools, vaccinations as per national guidelines, and use of inhaled bronchodilators for airflow obstruction.[74] The use of ICS in PTLD is not recommended as their use has been shown to increase the risk of both lower respiratory tract infections, including of mycobacteria other than tuberculosis, and recurrence of pTB-disease. Pulmonary rehabilitation may improve patient quality of life. [75]

Meeting the challenge

PTLD is associated with a single clearly defined exposure, and there is therefore an opportunity to identify those with disease at TB-treatment completion. Evidence is required to inform decisions about how this is should be done, which patients would benefit from ongoing follow-up, and the impact and cost-efficacy of clinical interventions for this group, before screening for PTLD is implemented in LMICs. In addition, the broader cardiovascular, psychological and socioeconomic morbidities faced by TB-survivors must also be addressed within any packages of post-TB care,[76] as well as improved approaches to the diagnosis of recurrent TB disease.

HEALTH SYSTEMS STRENGTHENING

Strong health systems which are capable of providing effective and efficient services across the care continuum will be key to the provision of NCD care in LMICs. Development of these will require attention to the 6 key 'building blocks' specified by the World Health Organization (WHO), including: (i) service delivery, (ii) health workforce, (iii) health information systems, (iv) access to essential medicines, (v) financing, and (vi) leadership/governance.[77] 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 remain sparse,[78] limiting the capacity of countries to identify and plan for the health care needs of their populations. Guidelines for the management of CRDs remain limited, and were identified in only 64% of countries in the 7th NCD country capacity survey 2019.[79] Crucially, the health workforce remains poorly equipped to deliver respiratory care, with numbers of respiratory specialists remaining low,[80-82] and most care delivered at the primary care level often by nursing staff.[83] Access to key diagnostic tools including spirometry and imaging is limited and in 2019 peak flow / spirometry were available in 45% of primary care facilities only, compared to 88% for blood glucose measurement.[79] 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 not siloed, but rather are efficiently integrated within broader services, and targeted to local needs. Several approaches to integrated care have been developed for use in LMICs.[84 85] Early models, such as the WHO Practical Approach to Lung Disease (PAL),[86] which was developed, in part, to improve case finding for TB, focussed only on respiratory diseases. These have been followed by tools with more comprehensive scope including the Package of Care Kit (PACK) for children, adolescents and adults.[87] PACK was developed in Cape Town and is now in use in South Africa,[88] Brazil,[89] Nigeria,[90] and other countries (www.knowledgetranslation.co.za). It includes a decision support tool for use across a range of clinical presentations and is available in both paper and

electronic tablet form. It integrates local management guidelines and evidence, and is updated almost annually to allow for this, and is supported by a continuous programme of on-site, case-based, interactive training.[91 92] Although not specifically focused on CRDs, 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.[91-93]

We indicate that respiratory and tuberculosis services should be closely linked in LMICs. Patients with CRDs frequently present with chronic or worsening respiratory symptoms and in high TB incidence 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 must be encouraged to incorporate palliative care support within their services. This is particularly important for CRDs which are frequently irreversible, progressive, and can be associated with distressing symptoms such as severe breathlessness in advanced stages. Integration of palliative care into CRD services will require cultural awareness, education of staff and patients, development of symptom management algorithms, and access to opioid medications.[94]

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, access to robust biomedical engineering support for maintenance, [95] and training in how to perform diagnostic tests, maintain quality control, and accurately interpret results. Some of these barriers will be lessened in the coming years, with advances in the development of robust portable spirometry equipment, and increasing investment in portable CXR for community-based TB diagnostics. However, education about the importance of equipment maintenance, and quality assurance of testing will be needed to deliver investigations such as spirometry in resource-constrained settings.[96] It is likely that more complex respiratory diagnostics such as CT imaging, full lung function testing, and bronchoscopy remain the purview of tertiary centres in LMICs, but these diagnostics are of value in the training and retention of specialist physicians and research capacity, and so 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),[97] access remains limited: in 2019, ICS were generally available in 19% of low-income countries compared to 96% of high-income countries, and the figures were 55% and 100% for bronchodilators. Even where available, respiratory medications were frequently not provided free of charge to patients, such that in LMICs they frequently remain inaccessible. For respiratory diseases, non-pharmacological interventions are also crucial. Pulmonary Rehabilitation (PR) and smoking cessation are among the most cost-effective interventions for chronic respiratory disease, and can be successfully adapted for delivery in LMICs, [75 98] but access remains limited. This is in part due to lack of awareness, but also limited support to modify these tools for local use, and to embed them within clinical care. Advocacy around access to both pharmacological and non-pharmacological interventions will be required if CRD outcomes are to be improved.

RESEARCH PRIORITIES & RESEARCH CAPACITY STRENGTHENING

This review has highlighted several areas of uncertainty which suggest research priorities to improve the management of 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 two respiratory focused training

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".[99 100] They also both offer three modules that cover topics including 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. Together, these courses have trained over 1000 participants from 90 countries, resulting in a large body of published literature that has been shown to contribute to changes in policy and practice.[101 102-105] Graduates have a strong track record of remaining in research after course completion,[106-109] or continuing on to become course faculty.[106-108 110]
3.

4. 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. The major determinants of CRD in LMICs that are amenable to intervention are: 1) poor maternal nutrition and health; 2) exposure to airborne contaminants (tobacco smoke, air pollution and occupational exposure to dust and fumes); and 3) severe or untreated respiratory infections including tuberculosis. Policy action directed at these causes of CRD will yield benefits in the short- and long-term. However, a substantial burden of disease will continue to exist and therapeutic strategies are required to mitigate suffering from breathlessness, cough, sputum production and activity limitation and to reduce the risk of severe attacks that impede the ability to work or study, require urgent medical care and may cause death. The UHC agenda should be co-opted and adapted to the needs of those suffering from CRD to ensure that they get affordable and sustained access to appropriate and effective diagnostic evaluation and to therapeutic interventions, both pharmacological and non-pharmacological. 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 settings, this likely to require resourcing and capacity building at the most peripheral level 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, approval of the version to be published and agreement to be accountable for all aspects of the work.

DECLARATION OF INTERESTS

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5. TABLES

Table 1: Essential medicines for CRD management[97]

Category	Drug
Respiratory medications	Beclomethasone
	Budesonide
	Budesonide + Formoterol
	Epinephrine (adrenaline)
	Ipratropium bromide
	Salbutamol – inhaled & nebulised
	Tiotropium
Antiallergics and medicines used in anaphylaxis	Prednisolone
Medical gases	Oxygen
Medicines for pain and palliative care	Opioid preparations (codeine, fentanyl, morphine)
Vaccines	Influenza vaccine (seasonal)
	Pneumococcal vaccine (conjugate & polysaccharide)

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	Birth cohorts in diverse settings in LMICs, to obtain prospective data on how genetic parameters, and in utero & early childhood exposures effect lung development.
	Investigation of the long-term impact of LRTI or 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
	Vaccines and new strategies to reduce childhood LRTI
Asthma	How can access to basic effective asthma care including access to affordable quality-assured SABA, ICS and ICS-formoterol be made available to everyone who needs it?
	Can the GINA-recommendation for as-required ICS-formoterol for steps 1 and 2 of asthma treatment be scaled-up in pragmatic way that accounts for difficulties in making a definitive diagnosis of asthma and the potential overlap with other diagnoses like COPD, TB and HIV?
COPD	Longitudinal data on patient-outcomes associated with airway obstruction in smokers and non-smokers in LMICs
	Investigation of the efficacy of pharmacological and non-pharmacological therapies for non-smoking related COPD in LMICs
Bronchiectasis	Data on the microbiology of bronchiectasis in LMICs, including colonising organisms, and those associated with exacerbations
	Investigation of the diagnosis and management of bronchiectasis in children in LMICs
Post-TB lung disease	Investigation of host, pathogen, and environmental risk factors for PTLD
	Longitudinal data on patient outcomes related to PTLD, including morbidity and mortality
	Investigation of the performance of TB diagnostic tools in those with PTLD being investigated for recurrent TB disease
CRD diagnosis	Consensus guidelines for the quality control of spirometry performed in routine clinical practice in LMICs settings
	Consensus guidelines for the standardisation of spirometry in LMICs, and use of reference ranges

CRD management	Investigation of pathogens causing respiratory exacerbations of CRDs in LMICs, to inform antibiotic guidelines and vaccine use.
	Adaptation of non-pharmacological CRD management tools for use in LMICs, including 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 LMICs in international CRD registries and consensus statements regarding global CRD research priorities
Health systems	Methods for programmatic data capture, to contribute data on the burden and nature of CRDs in LMICs, and to allow for local service planning
	Models of integrated CRD care in LMICs, which are: - Co-developed with patients and responsive to patient needs - Integrated with TB services - Integrated with palliative care services With tools for the evaluation of clinical impact, and health system / patient costs.
Respiratory training	Core curriculum for clinical respiratory training in LMICs

6. REFERENCES

1. Bennett JE, Stevens GA, Mathers CD, et al. NCD Countdown 2030: worldwide trends in non-communicable disease mortality and progress towards Sustainable Development Goal target 3.4. *The Lancet* 2018;392(10152):1072-88.
2. Ezzati M, Pearson-Stuttard J, Bennett JE, et al. Acting on non-communicable diseases in low- and middle-income tropical countries. *Nature* 2018;559(7715):507-16.
3. Bush A. Lung Development and Aging. *Annals of the American Thoracic Society* 2016;13 Suppl 5:S438-s46.
4. Agustí A, Noell G, Brugada J, et al. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. *The Lancet Respiratory Medicine* 2017;5(12):935-45.
5. Gray D, Willemse L, Visagie A, et al. Determinants of early-life lung function in African infants. *Thorax* 2017;72(5):445-50.
6. Agrawal A, Aggarwal M, Sonnappa S, et al. Ethnicity and spirometric indices: hostage to tunnel vision? *Lancet Respir Med* 2019;7(9):743-44.
7. Burney PG, Hooper R. Forced vital capacity, airway obstruction and survival in a general population sample from the USA. *Thorax* 2011;66(1):49-54.
8. Burney P, Jithoo A, Kato B, et al. Chronic obstructive pulmonary disease mortality and prevalence: the associations with smoking and poverty--a BOLD analysis. *Thorax* 2014;69(5):465-73.
9. Gray DM, Turkovic L, Willemse L, et al. Lung Function in African Infants in the Drakenstein Child Health Study. Impact of Lower Respiratory Tract Illness. *Am J Respir Crit Care Med* 2017;195(2):212-20.
10. Lee AG, Kaali S, Quinn A, et al. Prenatal Household Air Pollution Is Associated with Impaired Infant Lung Function with Sex-Specific Effects. Evidence from GRAPHS, a Cluster Randomized Cookstove Intervention Trial. *Am J Respir Crit Care Med* 2019;199(6):738-46.

11. MacGinty RP, Kariuki SM, Barnett W, et al. Associations of antenatal maternal psychological distress with infant birth and development outcomes: Results from a South African birth cohort. *Comprehensive psychiatry* 2020;96:152128.
12. Gray DM, Wedderburn CJ, MacGinty RP, et al. Impact of HIV and antiretroviral drug exposure on lung growth and function over 2 years in an African Birth Cohort. *AIDS (London, England)* 2019
13. Famoroti T, Sibanda W, Ndung'u T. Prevalence and seasonality of common viral respiratory pathogens, including Cytomegalovirus in children, between 0-5 years of age in KwaZulu-Natal, an HIV endemic province in South Africa. *BMC pediatrics* 2018;18(1):240.
14. Tran DN, Trinh QD, Pham NT, et al. Clinical and epidemiological characteristics of acute respiratory virus infections in Vietnamese children. *Epidemiol Infect* 2016;144(3):527-36.
15. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008;178(7):667-72.
16. Zar HJ, Barnett W, Stadler A, et al. Aetiology of childhood pneumonia in a well vaccinated South African birth cohort: a nested case-control study of the Drakenstein Child Health Study. *The Lancet Respiratory Medicine* 2016;4(6):463-72.
17. World Health Organisation. Global Tuberculosis Report, 2019. Geneva, Switzerland.
18. Ferrand RA, Desai SR, Hopkins C, et al. Chronic lung disease in adolescents with delayed diagnosis of vertically acquired HIV infection. *Clin Infect Dis* 2012;55(1):145-52.
19. Masekela R, Anderson R, Moodley T, et al. HIV-related bronchiectasis in children: an emerging spectre in high tuberculosis burden areas. *Int J Tuberc Lung Dis* 2012;16(1):114-9.
20. Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. *The Lancet* 2013;382(9890):427-51.
21. Forno E, Weiner DJ, Mullen J, et al. Obesity and Airway Dysanapsis in Children with and without Asthma. *Am J Respir Crit Care Med* 2017;195(3):314-23.
22. Heinzerling AP, Guarnieri MJ, Mann JK, et al. Lung function in woodsmoke-exposed Guatemalan children following a chimney stove intervention. *Thorax* 2016;71(5):421-8.
23. Rylance S, Nightingale R, Naunje A, et al. Lung health and exposure to air pollution in Malawian children (CAPS): a cross-sectional study. *Thorax* 2019;74(11):1070-77.
24. Soriano JB, Abajobir AA, Abate KH, et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med* 2017;5(9):691-706.
25. Global Initiative for Asthma. Global strategy for asthma management and prevention, 2019. Available from www.ginasthma.org. 2019
26. The Global Asthma Network. Global Asthma Report 2018. New Zealand, 2018.
27. British Thoracic Society. British guideline for the management of asthma: A national clinical guideline: British Thoracic Society / NHS Scotland.
28. Ade G, Gninafon M, Tawo L, et al. Management of asthma in Benin: the challenge of loss to follow-up. *Public Health Action* 2013;3:76-80.
29. El Sony AI, Chiang CY, Malik E, et al. Standard case management of asthma in Sudan: a pilot project. [Erratum appears in Public Health Action 2014;4:134]. *Public Health Action* 2013;3:247-52.
30. Chiang CY, Aït-Khaled N, Bissell K, et al. Management of asthma in resource-limited settings: role of low-cost corticosteroid/β-agonist combination inhaler. [State of the art series. The global burden of chronic respiratory disease. Number 4 in the series]. *Int J Tuberc Lung Dis* 2015;19:129-36.
31. Reddel HK, FitzGerald JM, Bateman ED, et al. GINA 2019: a fundamental change in asthma management. *Eur Respir J* 2019;53(6):1901046.
32. Bateman ED, Reddel HK, O'Byrne PM, et al. As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma. *New Engl J Med* 2018;378(20):1877-87.
33. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma. *New Engl J Med* 2018;378(20):1865-76.

34. Beasley R, Holliday M, Reddel HK, et al. Controlled Trial of Budesonide–Formoterol as Needed for Mild Asthma. *New Engl J Med* 2019;380(21):2020-30.
35. Hardy J, Baggott C, Fingleton J, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. *Lancet* 2019;394(10202):919-28.
36. World Health Organization. 20th WHO Model List of Essential Medicines (March 2017). Available from https://www.who.int/medicines/publications/essentialmedicines/20th_EML2017_FINAL_amendedAug2017.pdf. 2017
37. Menezes AM, Perez-Padilla R, Jardim JR, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. *Lancet* 2005;366(9500):1875-81.
38. Caballero A, Torres-Duque CA, Jaramillo C, et al. Prevalence of COPD in five Colombian cities situated at low, medium, and high altitude (PREPOCOL study). *Chest* 2008;133(2):343-9.
39. Echazarreta AL, Arias SJ, Del Olmo R, et al. Prevalence of COPD in 6 Urban Clusters in Argentina: The EPOC.AR Study. *Archivos de bronconeumologia* 2018;54(5):260-69.
40. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study. *The Lancet* 2007;370(9589):741-50.
41. Obaseki DO, Erhabor GE, Gnatiuc L, et al. Chronic Airflow Obstruction in a Black African Population: Results of BOLD Study, Ile-Ife, Nigeria. *Copd* 2016;13(1):42-9.
42. Meghji J, Nadeau G, Davis KJ, et al. Noncommunicable Lung Disease in Sub-Saharan Africa. A Community-based Cross-Sectional Study of Adults in Urban Malawi. *Am J Respir Crit Care Med* 2016;194(1):67-76.
43. Woldeamanuel GG, Mingude AB, Geta TG. Prevalence of chronic obstructive pulmonary disease (COPD) and its associated factors among adults in Abeshge District, Ethiopia: a cross sectional study. *BMC Pulm Med* 2019;19(1):181.
44. Perez-Padilla R, Fernandez R, Lopez Varela MV, et al. Airflow obstruction in never smokers in five Latin American cities: the PLATINO study. *Archives of medical research* 2012;43(2):159-65.
45. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet* 2009;374(9691):733-43.
46. Lamprecht B, McBurnie MA, Vollmer WM, et al. COPD in Never Smokers: Results From the Population-Based Burden of Obstructive Lung Disease Study. *Chest* 2011;139(4):752-63.
47. Lange P, Celli B, Agusti A. Lung-Function Trajectories and Chronic Obstructive Pulmonary Disease. *The New England journal of medicine* 2015;373(16):1575.
48. Talamo C, de Oca MM, Halbert R, et al. Diagnostic labeling of COPD in five Latin American cities. *Chest* 2007;131(1):60-7.
49. Casas Herrera A, Montes de Oca M, Lopez Varela MV, et al. COPD Underdiagnosis and Misdiagnosis in a High-Risk Primary Care Population in Four Latin American Countries. A Key to Enhance Disease Diagnosis: The PUMA Study. *PLoS One* 2016;11(4):e0152266.
50. Lamprecht B, Soriano JB, Studnicka M, et al. Determinants of underdiagnosis of COPD in national and international surveys. *Chest* 2015;148(4):971-85.
51. Lopez Varela MV, Muino A, Perez Padilla R, et al. [Treatment of chronic obstructive pulmonary disease in 5 Latin American cities: the PLATINO study]. *Archivos de bronconeumologia* 2008;44(2):58-64.
52. Montes de Oca M, Talamo C, Perez-Padilla R, et al. Use of respiratory medication in five Latin American cities: The PLATINO study. *Pulmonary pharmacology & therapeutics* 2008;21(5):788-93.
53. Jardim JR, Stirbulov R, Moreno D, et al. Respiratory medication use in primary care among COPD subjects in four Latin American countries. *Int J Tuberc Lung Dis* 2017;21(4):458-65.
54. Vanjare N, Chhowala S, Madas S, et al. Use of spirometry among chest physicians and primary care physicians in India. *NPJ primary care respiratory medicine* 2016;26:16036.

55. Grigsby MR, Siddharthan T, Pollard SL, et al. Low Body Mass Index Is Associated with Higher Odds of COPD and Lower Lung Function in Low- and Middle-Income Countries. *Copd* 2019;16(1):58-65.
56. Singh SJ, Halpin DMG, Salvi S, et al. Exercise and pulmonary rehabilitation for people with chronic lung disease in LMICs: challenges and opportunities. *The Lancet Respiratory Medicine* 2019;7(12):1002-04.
57. Quaderi SA, Hurst JR. The unmet global burden of COPD. *Glob Health Epidemiol Genom* 2018;3:e4.
58. Dhar R, Singh S, Talwar D, et al. Bronchiectasis in India: results from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) and Respiratory Research Network of India Registry. *The Lancet Global health* 2019;7(9):e1269-e79.
59. Chandrasekaran R, Mac Aogain M, Chalmers JD, et al. Geographic variation in the aetiology, epidemiology and microbiology of bronchiectasis. *BMC Pulm Med* 2018;18(1):83.
60. Shoemark A, Ozerovitch L, Wilson R. Aetiology in adult patients with bronchiectasis. *Respir Med* 2007;101(6):1163-70.
61. Chang AB, Brown N, Toombs M, et al. Lung disease in indigenous children. *Paediatric respiratory reviews* 2014;15(4):325-32.
62. Boaventura R, Sibila O, Agusti A, et al. Treatable traits in bronchiectasis. *Eur Respir J* 2018;52(3)
63. Allwood BW, Myer L, Bateman ED. A systematic review of the association between pulmonary tuberculosis and the development of chronic airflow obstruction in adults. *Respiration; international review of thoracic diseases* 2013;86(1):76-85.
64. Byrne AL, Marais BJ, Mitnick CD, et al. Tuberculosis and chronic respiratory disease: a systematic review. *Int J Infect Dis* 2015;32:138-46.
65. Amaral AF, Coton S, Kato B, et al. Tuberculosis associates with both airflow obstruction and low lung function: BOLD results. *Eur Respir J* 2015;46(4):1104-12.
66. Meghji J, Simpson H, Squire SB, et al. A Systematic Review of the Prevalence and Pattern of Imaging Defined Post-TB Lung Disease. *PLoS One* 2016;11(8):e0161176.
67. Romanowski K, Baumann B, Basham CA, et al. Long-term all-cause mortality in people treated for tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2019;19(10):1129-37.
68. Dorman SE, Schumacher SG, Alland D, et al. Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *The Lancet Infectious Diseases* 2018;18(1):76-84.
69. Kendall EA, Schumacher SG, Denkinger CM, et al. Estimated clinical impact of the Xpert MTB/RIF Ultra cartridge for diagnosis of pulmonary tuberculosis: A modeling study. *PLoS medicine* 2017;14(12):e1002472.
70. Metcalfe JZ, Mason P, Mungofa S, et al. Empiric tuberculosis treatment in retreatment patients in high HIV/tuberculosis-burden settings. *Lancet Infect Dis* 2014;14(9):794-95.
71. Houben R, Lalli M, Kranzer K, et al. What if They Don't Have Tuberculosis? The Consequences and Trade-offs Involved in False-positive Diagnoses of Tuberculosis. *Clin Infect Dis* 2019;68(1):150-56.
72. van Kampen SC, Wanner A, Edwards M, et al. International research and guidelines on post-tuberculosis chronic lung disorders: a systematic scoping review. *BMJ Glob Health* 2018;3(4):e000745.
73. Harries AD, Dlodlo RA, Brigden G, et al. Should we consider a 'fourth 90' for tuberculosis? *Int J Tuberc Lung Dis* 2019
74. The Union. Management of Tuberculosis: A Guide to Essential Practice. 7th Edition ed. Paris, France: The International Union against Tuberculosis and Lung Disease.
75. Jones R, Kirenga BJ, Katagira W, et al. A pre-post intervention study of pulmonary rehabilitation for adults with post-tuberculosis lung disease in Uganda. *International journal of chronic obstructive pulmonary disease* 2017;12:3533-39.

76. Ranzani OT, Rodrigues LC, Bombarda S, et al. Long-term survival and cause-specific mortality of patients newly diagnosed with tuberculosis in São Paulo state, Brazil, 2010–15: a population-based, longitudinal study. *The Lancet Infectious Diseases* 2020;20(1):123-32.
77. World Health Organisation. Monitoring the building blocks of health systems: A handbook of indicators and their measurement strategies. Geneva, Switzerland, 2010.
78. Buist AS, Parry V. The American Thoracic Society methods in epidemiologic, clinical, and operations research program. A research capacity-building program in low- and middle-income countries. *Annals of the American Thoracic Society* 2013;10(4):281-9.
79. World Health Organisation. Assessing national capacity for the prevention and control of noncommunicable diseases: Report of the 2017 Global Survey. Geneva, Switzerland, 2018.
80. Obaseki D, Adeniyi B, Kolawole T, et al. Gaps in capacity for respiratory care in developing countries. Nigeria as a case study. *Annals of the American Thoracic Society* 2015;12(4):591-8.
81. Wilmshurst JM, Morrow B, du Preez A, et al. The African Pediatric Fellowship Program: Training in Africa for Africans. *Pediatrics* 2016;137(1)
82. Zar HJ, Vanker A, Gray D, et al. The African Pediatric Fellowship Training Program in Pediatric Pulmonology: A Model for Growing African Capacity in Child Lung Health. *Annals of the American Thoracic Society* 2017;14(4):500-04.
83. Mash B, Fairall L, Adejayan O, et al. A morbidity survey of South African primary care. *PLoS One* 2012;7(3):e32358.
84. Cornick R, Picken S, Wattrus C, et al. The Practical Approach to Care Kit (PACK) guide: developing a clinical decision support tool to simplify, standardise and strengthen primary healthcare delivery. *BMJ Glob Health* 2018;3(Suppl 5):e000962.
85. Fairall L, Cornick R, Bateman E. Empowering frontline providers to deliver universal primary healthcare using the Practical and Approach to care kit. *BMJ Glob Health* 2018;3(Suppl 5)
86. WHO Guidelines Approved by the Guidelines Review Committee. Practical Approach to Lung Health: Manual on Initiating PAL Implementation. Geneva: World Health Organization

87. Picken S, Hannington J, Fairall L, et al. PACK Child: the development of a practical guide to extend the scope of integrated primary care for children and young adolescents. *BMJ Glob Health* 2018;3(Suppl 5):e000957.
88. Cornick R, Wattrus C, Eastman T, et al. Crossing borders: the PACK experience of spreading a complex health system intervention across low-income and middle-income countries. *BMJ Glob Health* 2018;3(Suppl 5):e001088.
89. Wattrus C, Zepeda J, Cornick RV, et al. Using a mentorship model to localise the Practical Approach to Care Kit (PACK): from South Africa to Brazil. *BMJ Glob Health* 2018;3(Suppl 5):e001016.
90. Awotiwon A, Sword C, Eastman T, et al. Using a mentorship model to localise the Practical Approach to Care Kit (PACK): from South Africa to Nigeria. *BMJ Glob Health* 2018;3(Suppl 5):e001079.
91. Zwarenstein M, Fairall LR, Lombard C, et al. Outreach education for integration of HIV/AIDS care, antiretroviral treatment, and tuberculosis care in primary care clinics in South Africa: PALSA PLUS pragmatic cluster randomised trial. *BMJ (Clinical research ed)* 2011;342:d2022.
92. Fairall L, Bachmann MO, Zwarenstein M, et al. Cost-effectiveness of educational outreach to primary care nurses to increase tuberculosis case detection and improve respiratory care: economic evaluation alongside a randomised trial. *Tropical medicine & international health : TM & IH* 2010;15(3):277-86.
93. Fairall LR, Folb N, Timmerman V, et al. Educational Outreach with an Integrated Clinical Tool for Nurse-Led Non-communicable Chronic Disease Management in Primary Care in South Africa: A Pragmatic Cluster Randomised Controlled Trial. *PLoS medicine* 2016;13(11):e1002178.
94. Hannon B. Provision of Palliative Care in Low- and Middle-Income Countries: Overcoming Obstacles For Effective Treatment Delivery.

95. Fonjungo PN, Kebede Y, Messele T, et al. Laboratory equipment maintenance: a critical bottleneck for strengthening health systems in sub-Saharan Africa? *Journal of public health policy* 2012;33(1):34-45.
96. Masekela R, Hall GL, Stanojevic S, et al. An urgent need for African spirometry reference equations: the Paediatric and Adult African Spirometry study. *Int J Tuberc Lung Dis* 2019;23(8):952-58.
97. World Health Organisation. World Health Organization Model List of Essential Medicines: 21st List 2019. Geneva, Switzerland, 2019.
98. Jones R, Muyinda H, Nyakoojo G, et al. Does pulmonary rehabilitation alter patients' experiences of living with chronic respiratory disease? A qualitative study. *International journal of chronic obstructive pulmonary disease* 2018;13:2375-85.
99. Zachariah R, Harries AD, Ishikawa N, et al. Operational research in low-income countries: what, why, and how? *Lancet Infect Dis* 2009;9(11):711-7.
100. Ramsay A, Harries AD, Zachariah R, et al. The Structured Operational Research and Training Initiative for public health programmes. *Public Health Action* 2014;4(2):79-84.
101. Zachariah R, Rust S, Berger SD, et al. Building Global Capacity for Conducting Operational Research Using the SORT IT Model: Where and Who? *PLoS One* 2016;11(8):e0160837.
102. Tripathy JP, Kumar AM, Guillerm N, et al. Does the Structured Operational Research and Training Initiative (SORT IT) continue to influence health policy and/or practice? *Global health action* 2018;11(1):1500762.
103. Kumar AM, Zachariah R, Satyanarayana S, et al. Operational research capacity building using 'The Union/MSF' model: adapting as we go along. *BMC research notes* 2014;7:819.
104. Sagili KD, Satyanarayana S, Chadha SS, et al. Operational research within a Global Fund supported tuberculosis project in India: why, how and its contribution towards change in policy and practice. *Global health action* 2018;11(1):1445467.
105. Zachariah R, Guillerm N, Berger S, et al. Research to policy and practice change: is capacity building in operational research delivering the goods? *Tropical medicine & international health : TM & IH* 2014;19(9):1068-75.
106. Guillerm N, Dar Berger S, Bissell K, et al. Sustained research capacity after completing a Structured Operational Research and Training (SORT IT) course. *Public Health Action* 2016;6(3):207-08.
107. Guillerm N, Tayler-Smith K, Berger SD, et al. What happens after participants complete a Union-MSF structured operational research training course? *Public Health Action* 2014;4(2):89-95.
108. Guillerm N, Tayler-Smith K, Dar Berger S, et al. Research output after participants complete a Structured Operational Research and Training (SORT IT) course. *Public Health Action* 2015;5(4):266-8.
109. Bissell K, Harries AD, Reid AJ, et al. Operational research training: the course and beyond. *Public Health Action* 2012;2(3):92-7.
110. Fatima R, Yaqoob A, Qadeer E, et al. Building sustainable operational research capacity in Pakistan: starting with tuberculosis and expanding to other public health problems. *Global health action* 2019;12(1):1555215.