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Review Article

Africa's respiratory "Big Five"

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ABSTRACT

The British Thoracic Society (BTS) launched a Global Health Group in the winter of 2019 in partnership with the Pan African Thoracic Society. This key meeting generated a lot of interest and areas of mutual benefit. Due to the overwhelming interest at the 2019 meeting, a virtual offering of the BTS Winter meeting February 2021, included a symposium by the Global Health Group on Africa's Respiratory "Big Five." The Winter meeting was free for PATS members and symposium had an excellent attendance, covering the following areas: Pneumonia in the under 5, impact of air pollution on lung health, post-TB lung disease, and non-communicable respiratory disease across the life course. This paper is a summary of the symposium and seeks to address research priority areas for lung health research on the African continent.

Keywords: Pneumonia in the under 5, Air pollution, Post-TB lung disease, Non-communicable respiratory disease, Research priorities

INTRODUCTION

The British Thoracic Society (BTS) launched a Global Health Group at the 2019 Winter Meeting in Partnership with the Pan African Thoracic Society (PATS). This was met with an overwhelming level of interest and a symposium on Africa's Respiratory "Big Five" was proposed in response and to build on the momentum behind the Global Health Group. Whilst 2020 turned out to be a rather different year to that expected when we convened at the end of 2019, we continued our work to the best of our ability and delivered our symposium at the rescheduled BTS Winter Meeting in February 2021 in a virtual format. We were delighted by the level of interest in the symposium which had 226 attendees. We were deeply grateful to the BTS for extending an offer of free registration and attendance at the full Winter Meeting to all PATS members. This paper offers a summary of the symposium focused on research priorities relating to the topics discussed (pneumonia in the under fives, post-TB lung disease, ambient air pollution (AP), and respiratory disease and non-communicable respiratory disease across the life-course). It then links this to PATS Methods in Epidemiologic Clinical and Operations Research (MECOR) in the hope this will stimulate new ideas for PATS MECOR student projects and possible projects that BTS and PATS members could do together.

PNEUMONİA İN UNDER-FİVES

For decades, pneumonia has persistently remained the biggest killer of children but is still forgotten. In 2018, an estimated 802,000 children age <5 years died from pneumonia. Low- and middle-income countries, especially those in sub-Saharan Africa and South-East Asia (SEA), are disproportionately affected, with up to 99% of the pneumonia cases and deaths occurring in these countries.[1,2] Between 2000 and 2018, pneumonia deaths reduced by 54% but this progress is slower compared to reductions in other childhood infectious diseases such as measles (81%), HIV (67%), diarrhea (64%), and malaria (59%).[3]

Pneumonia deaths are largely preventable. The integrated Global Action Plan for Pneumonia and Diarrhea aims to reduce pneumonia deaths to less than 3/1000 live births globally.[3] However, given the current trends, the world will not meet this target. Many countries in Africa including Nigeria, Democratic Republic of Congo, and Tanzania have a high pneumonia burden with less than 10% annual rate of reduction in pneumonia deaths.[4] The poorest and most vulnerable children are at greatest risk; therefore, pneumonia is a marker of health inequities and multiple deprivations. Furthermore, recurrent pneumonia in early childhood increases the risk of developing chronic lung diseases such as asthma and chronic obstructive pulmonary disease (COPD).[5,6]

Interventions to prevent pneumonia deaths include; (1) protecting children from getting pneumonia through adequate nutrition, (2) comprehensive immunization against pneumococcus, measles, *Haemophilus influenzae* type b, pertussis (whooping cough), and influenza, (3) avoiding tobacco smoke exposure and reducing exposure to indoor AP, and (4) prevention and treatment of HIV. Children who get pneumonia can also be saved if prompt and appropriate treatment with antibiotics, referral to hospital, and oxygen therapy when needed are provided. However, despite these interventions, pneumonia deaths remain unacceptably high and the problem is multifactorial. Africa has a high burden of risk factors for pneumonia. Up to 35% of deaths in under-fives are associated with malnutrition, and the case-fatality rate among severely malnourished children with pneumonia ranges between 17 and 37.6%.[1,7-9] Less than 10% of children are exclusively breastfed for 4–6 months.[10-12] Vaccines such as the pneumococcal conjugate vaccine (PCV) are very effective in prevention of pneumonia. In Malawi, the introduction of the 13-valent PCV led to a decline of hypoxemic pneumonia and overall childhood deaths by 47% and 36%, respectively,[13] while in The Gambia, the incidence of invasive pneumococcal disease decreased by 55%.[14] However, one in five children in Africa does not receive the vaccines they need. Half of the pneumonia deaths are attributable to AP. In Africa, 95% of the children <5 years are exposed to high levels of AP largely from use of biomass for cooking[15] Interventions to reduce household AP through use of cleaner biomass fuelled cookstoves have been tried, but these have not significantly reduced the AP and as such, no significant impact on the incidence of childhood pneumonia.[16] The WHO/UNICEF Integrated Management of Childhood Illnesses and integrated Community Case Management strategies have played a big role in reducing pneumonia deaths in children.[17] However, access to care remains a challenge with only two-thirds of children who need antibiotics accessing them. Hypoxemia is a strong predictor of pneumonia deaths and using clinical evaluation alone is not sufficient to identify children with hypoxemia thus the need for widespread use of pulse oximetry.[18] Access to pulse oximetry and reliable oxygen delivery systems is a big challenge especially in remote health facilities.[18,19]

Previously, *Streptococcus pneumoniae* and *Haemophilus influenzae* were the major pathogens for severe pneumonia requiring hospitalization, but viruses are emerging as the leading cause of severe pneumonia. The Pneumonia Etiology Research Child Study[20] and the Drakenstein Child Health Study in South Africa have shown that RSV is responsible for up to 30% of the pneumonia cases, and that it was associated with a 3-fold risk of the lower respiratory tract infection (LRTI) thus increasing the risk of poor lung function.[21]

We know what works, but to accelerate the decline in pneumonia deaths, we must deliver innovative and comprehensive strategies to implement evidence-based interventions. The three pillars of Primary Health Care; Integrated Health Services, Multisectoral policy and action, and Empowered people and communities have been identified as the foundation for ending preventable child deaths from pneumonia. It is envisaged that pneumonia deaths can be substantially reduced if AP, nutrition, immunization, and case management including effective referral systems are comprehensively addressed. Despite being the leading cause of childhood deaths, pneumonia receives less development assistance than other diseases like HIV and malaria. There is need to increase allocation of funds to pneumonia control. Finally, accountability and engagement of communities and education are critical areas that will support and sustain pneumonia control strategies.

Three suggested research priorities

- Innovative ways to strengthen, accelerate, and sustain available interventions for pneumonia control
- Simple and cheap point of care diagnostics for pneumonia
- Explore mHealth and eHealth platforms.

POST-TB LUNG DİSEASE

The global burden of TB disease remains unacceptably high with an estimated 10 million incident cases and 1.4 million deaths in 2019.[22] However, survival is increasing and it is

now thought that 85% of TB patients survive to treatment completion, with an estimated 155 million TB survivors alive globally today, the majority of whom are located in the SEA, Western Pacific, and African WHO regions.[23] However, targets set by the international TB community and National TB programs, and estimates of TB-related morbidity remain focused on the period of TB disease and treatment only, with an assumption that the health of TB survivors returns to normal at TB treatment completion. In the current model of care patients are discharged at treatment completion with no rehabilitation, little health-care advice, and no further routine review. However, it is increasingly clear that for many patients, the long-term impact of TB disease on is marked.[24,25]

Post-TB lung disease (PTLD) is a key form of post-TB morbidity, alongside other forms of physical, psychosocial, and economic sequelae of disease. Several cross-sectional studies have demonstrated an association between previous TB disease and reduced lung function: Routine spirometry data from miners in South Africa shows that adults who had a previous episode of TB disease had forced expiratory volume (FEV_1) and forced vital capacity (FVC) volumes which were on average 180 ml and 120 ml lower that that seen in miners with no history of TB disease;[26] data from Malawi suggest that 3-years after TB treatment completion, 12.5% of PTB survivors had a low-FVC pattern of spirometry, and 15.8% had obstruction; findings from the burden of obstructive lung disease study showed that amongst 14,050 adults ≥40 years, drawn from 19 global study sites, a self-reported a history of TB disease was associated with both air-flow obstruction (aOR 2.51, 1.83–3.42) and spirometric restriction (aOR 2.13, 1.42–3.19);[27] and a recent cohort study of adult TB-survivors in South Africa suggests a high burden of gas trapping and impaired gas transfer amongst PTB survivors 1-year after TB-treatment completion.[28] A high burden of PTLD has also been demonstrated on imaging studies: Work in Malawi showed residual bronchiectasis and lobar parenchymal destruction in 44% and 9% of PTB survivors, respectively,[29] and these findings are consistent with systematic review data from elsewhere.[30] Marked heterogeneity in the patterns and extent of PTLD, and the extent to which the airways, parenchyma, pleura are affected by TB disease is observed across studies. This heterogeneity was discussed at the first international post-TB symposium held in 2019 at which a broad minimum case definition for PTLD was reached: Evidence of chronic respiratory abnormality, with or without symptoms, attributable at least in part to the previous tuberculosis.[31]

Understanding of the longer-term impact of PTLD on patient outcomes is growing. Prospective data tracking spirometry over time after PTB treatment completion suggests some recovery within the first 6–12 months after treatment completion, but shows that this recovery is incomplete. Similar findings are seen with data on symptoms, with a reduction in the frequency and prevalence of respiratory symptoms including cough and breathlessness from TB treatment completion to 6- and 12-months later, but still 10–20% of patients experiencing symptoms which affect daily activities or work in the Malawian cohort described above by 1-year.[29] Cross-sectional data from post-TB patients surveyed in one Indian setting identified breathlessness in almost a third of PTB survivors located 14–18 years after treatment completion.[32] It is possible that these ongoing post-TB respiratory symptoms and abnormal spirometry are associated with loss of work by 1 year after TB treatment completion.[33]

Other potential outcomes of concern amongst PTB survivors include recurrent TB disease, superadded respiratory infections, and increased mortality. Former TB patients are at high risk of recurrent TB disease, including both relapse and reinfection.[34,35] Rates of recurrence among PTB patients are three to four-fold higher than incidence rates seen in the general population in settings such as South Africa,[36,37] in both HIV-infected and HIV-negative adults.[37] However, the extent to which PTLD acts as a risk factor for disease recurrence remains unclear. Similarly, adults previously treated for TB disease have an increased standardized mortality rate for all-cause mortality compared to TB naïve adults, but the contribution of PTLD to long-term mortality remains unclear.[38] Although superimposed respiratory infections are observed in those with severe PTLD and destroyed lung,[39,40] the incidence and microbiology of these infections remain poorly described, and few primary data are available on the burden of fungal disease in LMICs.

Further research into approaches for prevention and management of PTLD are required. A more detailed understanding of the host, pathogen and environmental drivers of disease heterogeneity will be key to preventing TB patients from developing PTLD.[41,42] For those with established disease, evidence is needed for programmatic interventions which could be implemented in decentralized low-income settings to improve patient outcomes. Pulmonary rehabilitation holds much promise, with pilot work showing improvement in exercise capacity and quality of life among PTB survivors, and randomized trials are ongoing.[43,44] The development of digital rehabilitation tools in the COVID-19 era has the potential to increase accessibility.[45] More data are needed to determine whether post-TB obstructive airways disease should be managed similarly to tobacco related airway obstruction, and what the role of inhaled bronchodilators and steroids might be.[46] Crucially, the need to address the broader social determinants of health and disability must not be forgotten when thinking of strategies for post-TB care.[47,48]

Three suggested research priorities

- Collection of data on post-TB morbidity within broader TB research studies, including those focused on active case finding and TB treatment regimens
- Basic science and epidemiology research to understand the host, pathogen, and environmental determinants of the heterogeneity observed in PTLD, and to inform strategies for prevention
- Qualitative work to understand patient experiences and priorities for post-TB care in LMICs.

AİR POLLUTİON AND RESPİRATORY DİSEASE İN AFRİCA

AP has been deemed a "silent public health emergency" by the World Health Organization (WHO), akin to active, and passive tobacco exposure. Globally, more than 90% of the world's population live in areas with AP above WHO limits, with more than 7 million deaths attributed to AP annually.[49] AP affects LMIC disproportionately especially in Africa where there are a number of colliding epidemics, including a high burden of exposures, infectious diseases, and increasingly recognized non-communicable diseases.[50]

AP encompasses both indoor (household AP from the use of dirty-burning fuels for energy) and outdoor (generated by traffic, industry, and agriculture) sources.[51] The impact of AP on respiratory health begins early and continues throughout the life-course. Antenatal exposure to AP is not only associated with an increased risk of respiratory infections[52] but also impacts on lung development and growth with lung function impairments described in early life.[53] Life-long respiratory impacts include the irritant effects of AP exposure (cough, increased phlegm, bronchial hyperresponsiveness, and infective exacerbations), increased risk of asthma symptoms and exacerbations, accelerated decline in lung function, and increased morbidity and mortality from COPD and lung cancer.[54]

There is limited epidemiological AP data from Africa and where data are available, measured AP levels are 10 to 20-fold higher than acceptable WHO thresholds,[50] and a leading risk factor for LRTI morbidity and mortality, especially in children.[55] Further, intervention studies to reduce AP exposure, in particular household AP, through the use of cleaner burning cookstoves, have found that while there was some reduction in AP exposure,[56] a single intervention alone did not reduce LRTI incidence significantly, highlighting the need for a multi-prong intervention approach.[16]

The COVID-19 pandemic has further highlighted the social disparities in health outcomes, especially in LMIC settings. The implementation of "lockdown" policies by many countries to curb the spread of SARS-COV2 infection saw significant reductions in global outdoor AP. However, for many people with sub-optimal living conditions prevalent in many African LMIC, confinement to homes only increased the exposure to indoor environmental exposures.[57]

While addressing AP exposure requires a multi-sectorial approach that should be spearheaded at government level, the role of the health care worker (HCW) should not be underestimated. HCW need to be informed on AP and consider it as a risk factor for respiratory diseases; participate in research to understand the impacts of AP exposure; prescribe simple, translational solutions to affected families that can reduce AP exposures; educate colleagues and students on the risks associated with AP exposure by including in teaching and curricula; and advocate for solutions to other sectors, decision, and policy makers.[58]

Three suggested research priorities

- Robust African epidemiological AP data that are representative of all countries/regions in Africa
- Longitudinal exposure health outcome data that utilize validated exposure and outcome assessments, beyond self-reported
- Effective and affordable interventions to reduce AP exposure that may require a multi-pronged approach.

NON-COMMUNİCABLE RESPİRATORY DİSEASE (ASTHMA AND COPD) ACROSS THE LİFE-COURSE

The environment is one of the key determinants of outcomes, and this is heterogeneous within and between countries; there are islands of affluence in LMICs and poverty in high income settings (HICs). Diseases given the same umbrella label may be phenotypically different in different environments;[59] for example, in Brazil, ascaris burden was more closely related to asthma than was atopy.[60] Most life course information has come from HIC birth cohorts. Asthma and COPD start early in childhood.[61,62] Adverse intra-uterine events set up the baby for long-term impaired respiratory health. Most studied is smoking in pregnancy, and the outcomes are low birth weight and prematurity; abnormal lung structure; abnormal immune function setting the child up for early respiratory infection; and sensitization to the effects of subsequent exposures in adult life. Children with asthma have airflow obstruction age 7 years, and 40% of this is determined antenatally.[63] Impaired lung function shortly after birth strongly associates with altered lung structure in the third decade, and asthma in the fourth decade of life.[64] Subsequent growth trajectories in the main show that lung function tracks into late middle age without catch-up growth.[65-68] Lung function decline after age 20–25 years relates most consistently to early life disadvantage rather than adult smoking,[69,70] dangerous though the latter is in other ways. COPD risk is greatest in those who fail to reach

the normal lung function plateau in their early 20s, but is also seen in those with accelerated decline.[71]

There are important differences reported from Africa compared with HICs. There are significantly higher prevalences of smoking in pregnancy, maternal HIV infection and alcohol use, household benzene exposure, and psychological stresses such as post-traumatic stress syndrome and intimate partner violence.[72,73] The burden of infection is very high, even in asymptomatic children (median five organisms from a nasopharyngeal swab).[74] By contrast with Perth,[75] Australia, severe LRTI was an independent risk factor for 1 year lung function.[5] Vertical transmission of HIV was virtually totally prevented in Drakenstein, but infants born to HIV positive mothers had early abnormal lung function.[76] In HIC, impaired spirometry is associated not merely with poor respiratory outcomes, but also premature cardiovascular and metabolic morbidity and mortality.[77] Whether this is the case in Africa is unknown but seems likely.

In summary, if LMICs (and HICs) want to prevent asthma and COPD, they must start by protecting the fetus and the newborn. It is no use focusing on adult life, or distributing medicines like inhaled corticosteroids, laudable as this is, if fundamental changes are to be made. Early insults are not merely harmful in themselves, but set the baby up to vulnerability to later adverse events. Africa has novel early risk factors including pollutants, HIV positive mothers, and severe adverse physical and psychological circumstances. Africa also has novel second hits including tuberculosis and HIV, both of which have long-term respiratory sequelae, with the scene likely set for sequelae by early life deprivation. We need effective legislation, which we know works, to protect these vulnerable populations if LMIC lung health across the life course is to improve. Sadly, it is too late for preventative approaches for the present generation.

Three suggested research priorities

- What interventions can be used to reduce environmental pollution, specifically within the home, including reducing smoking and vaping?
- What interventions other than immunizations can be put in place to reduce the burden of infection in LMICs?
- How can women in particular be supported to prevent exposure to psychological stress including intimate partner violence?

PATS MECOR AND OPPORTUNİTİES TO ADDRESS RESEARCH GAPS FOR AFRİCA'S BİG 5

The PATS MECOR program is well positioned to address the research needs that could improve outcome and drive policy change regarding Africa's big 5. Since 2007, PATS in partnership with the American Thoracic Society through the MECOR program has trained 254 students from across 22 African countries in the conduct of research. The annual week-long course led predominantly by African faculty is delivered at three levels with subsequent continuous mentorship post-course. The course has gone further and also delivers quality training on spirometry and air quality measurement to equip the students for the conduct of high impact research.

The aim of the PATS MECOR program has been to address global respiratory needs with focus on the local contexts where our students live and work. We are aware that the time has come for Africans to be at the forefront of identifying, highlighting and seeking solution to their local challenges. The scope of the program that ranges from measurement of the burden of disease to advanced clinical research training, to manuscript and grant writing provides an excellent opportunity to build the needed capacity to confront the research gaps regarding Africa's Big 5.

We analyzed our student database for students who enrolled in the PATS MECOR course from 2015 to 2020, to review the throughputs of the course [Tables 1 and 2]. Data collected included participant demographics, country of origin, number who completed each level and number of students who received small grants for research projects. For the students who completed all three levels of the course, we conducted a PubMed search of all publications linked to the MECOR student and categorized these into pre-MECOR and post-MECOR research outputs. From the research outputs, the most prolific researchers who published were those linked into national research or governmental agencies with linkages to larger international research collaborative work. The university researchers collaborated with MECOR students and faculty in publications and tended to also be first and last authors.

Table 1: Summary table of PATS MECOR students and progress from 2015 to 2019 (*n*=124).

Characteristic	Number/%
Age (mean in years/range)	38.5¶ (29–60)
Gender (male)	85 (68.0)
Number of countries	17
Completed Level 1	124 (100.0)
Completed Level 2	58 (46.8)
Completed Level 3	20 (16.1)
Number of grants awarded	21
Number of grant recipients	20*
Grant recipients completed L3	5 (25.0)
Years between L1 and L2 (Mean age in years/range)	1.6 (1–8)
Years between L2 and L3 (Mean age in years/range)	1.5 (1–3)

¶Age available in only 91 students; *(1 student received 2 small grants)

Table 2: Research outputs of students who completed all three levels of PATS MECOR from 2015 to 2020 (*n*=20).

Characteristic (*n*/%)	Average number publications	Total female	Average publications by gender (female)	Total male	Average publication by gender male	Total *n* (%)
Publications	10.5	77	11 (37.0)	132	10.2 (63.0)	209 (100.0)
Local journal	1.0	12	1.7 (60.0)	8	0.6 (40.0)	20 (9.6)
International	9.5	65	9.3 (34.0)	124	9.5 (66.0)	189 (90.4)
Post-MECOR	7.8	46	6.6 (29.0)	110	8.5 (71.0)	156 (74.6)
PATS Journal	0.2	1	0.1 (33.0)	2	0.2 (67.0)	3 (1.4)
PATS Collaborator	1.3	9	1.3 (36.0)	16	1.2 (64.0)	25 (11.0)
First Author	0.9	13	1,9 (72.0)	5	0.4 (28.0)	18 (8.6)

About a quarter of new cases of TB globally are reported in Africa, yet the burden of post-TB lung disease in Africa is not well documented.[78] The implication of absent data is that health system needs other than programmatic TB treatment are not prioritized and no clear pathway for subsequent care exists. These are underpinnings for expansion of our research focus at PATS MECOR toward quantifying this burden which dovetails into exploring care pathways, effective modalities of treatment and the conceptualization and testing of potential preventive strategies.

The now apparent high burden of asthma in Africa brings to the fore the emerging research needs for primordial, primary and secondary prevention.[79] We also need research that strengthens health systems across Africa to deliver appropriate asthma care. Harnessing previously successful strategies used in improving access to care in Africa such as task shifting, free access to medications, community outreaches, and free testing are worth exploring.[80]

Lung function data for African children which sets the stage for future pulmonary, cardiovascular, and all-cause mortality are generally lacking. These data are needed to drive policy regarding household cooking fuels, siting of schools, and lung function testing as part of regular growth screening.[81] PATS MECOR students are well equipped to lead this charge.

Non-tobacco associated COPD which is more prevalent in Africa is an area that needs both epidemiologic and clinical data.[82] The risk factors need to be teased out together with the clinical profile, disease course, and response to available treatment modalities. As Africa improves its immunization coverage to reduce childhood pneumonias, there is also need to conduct research that improves outcome for those who develop pneumonia.

Three suggested research capability building priorities

1. Create African led and delivered research hubs and centers of excellence that will provide supportive research environments for African clinicians and scientists
2. Develop research capacity building opportunities for graduates of programs like PATS MECOR including Masters, PhD Fellowships, and post-doctoral training posts
3. Monitor and evaluate the outcomes of PATS MECOR and other research capability building programs to identify areas for strengthening these and learn from barriers and facilitators of academic career development in Africa.

CONCLUSİON

There is a clear need to keep focused on the major causes of morbidity and mortality across the life-course in Africa and persevere with our efforts to make a difference despite the desperately difficult circumstances we all find ourselves in at the moment. COVID-19 was not a known disease when we launched the BTS Global Health Group in early December 2019. This symposium deliberately kept its original focus as COVID-19 has already taken so much from so many and that sadly includes resources from Africa's respiratory big five. Although the coming years will undoubtedly be difficult, initiatives that bring us together including our collaboration between PATS and the BTS Global Health Group offer much needed hope that we can and will make a difference.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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