Title page

**Bronchiectasis in African Children: disease burden, aetiology and clinical spectrum at a paediatric tertiary hospital in Cape Town, South Africa.**

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**Declaration**

I, Muntanga Kampengele Mapani, do hereby declare that this dissertation/thesis is based on my original work (except where acknowledgement indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. This dissertation has not been Reported or published anywhere prior to registration for the above-mentioned degree.
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Muntanga Kampengele Mapani conceived and designed the study and substantially contributed to data acquisition, analysis and interpretation, drafting the dissertation and final approval of the version submitted. Diane Gray substantially contributed to study conception, study design, data analysis, revising the dissertation critically for intellectual content and final approval of the submitted version. Leah Githinji Fergusson substantially contributed to study conception, study design, data analysis, revising the dissertation critically for intellectual content and final approval of the submitted version. Aneesa Vanker substantially contributed to data analysis, revising the dissertation critically for intellectual content and final approval of the submitted version. Marco Zampoli substantially contributed to data analysis, revising the dissertation critically for intellectual content and final approval of the submitted version

**ABSTRACT**

Childhood bronchiectasis is a common cause of chronic lung disease globally, particularly in lower-middle-income countries (LMIC). Data from LMIC is lacking. We aimed to describe the disease burden, aetiology, and clinical spectrum of bronchiectasis in children attending a tertiary hospital in Cape Town, South Africa.

**Methods**

Data was collected by chart review of all patients 3 months to 15 years attending the respiratory clinic at red cross war memorial children's hospital between January – December 2019. We included children who had a diagnosis of bronchiectasis based on history of a recurrent (> 3 episodes/year) or persistent (> 4 weeks) wet cough, a clinical phenotype characterized by any of; exertion dyspnea, recurrent chest infections, growth failure, finger clubbing and chest deformity associated with radiographic features of bronchiectasis on plain chest radiography or HRCT reported by a paediatric radiologist. Patients with cystic fibrosis were excluded.

**Results**

Of 337 children seen during the study period, 58 (17.2%) had bronchiectasis that was diagnosed at a mean age of 34 months (SD 26). There were 32 (55.0%) female participants. The commonest causes of bronchiectasis were post-infectious (25, 43.1%), and underlying immunodeficiencies (19, 32.8%) including 16/58 (27.6%) who were HIV-infected and 3 (5.1 %) with primary immunodeficiency. Other causes included aspiration syndrome (8, 13.8 %) and anatomical abnormalities (4, 6.9%). Of the participants with post infectious bronchiectasis, tuberculosis was the commonest organism that was isolated (16, 64.0%) and commonest in children living with HIV (11/16, 68.8%). Cough was common (48, 82.8%) with wet cough being predominant (41, 85.4%), course crepitations accounted for 37 (63.8%), hyperinflation 24 (41.4%) finger clubbing 21 (36.2%), wheeze 16 (29.3%) and exertional dyspnea in 7 (12.0%).

**Conclusion:** Bronchiectasis is a common cause of chronic lung disease in South African children mostly resulting from previous pneumonias, with tuberculosis being the commonest infective cause. The importance of identifying underlying treatable causes is highlighted.

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**List of Abbreviations**

| | |
|---|---|
| BC | Bronchiectasis |
| HRCT | High Resolution Computer Tomography |
| FEV1 | Forced Expiratory Volume in the first second |
| FVC | Forced Vital Capacity |
| BDR | Bronchodilator responsiveness |
| PCD | Primary Ciliary Dyskinesia |
| PID | Primary Immunodeficiency |
| RCWMCH | Red cross war memorial children's hospital |
| RSV | Respiratory syncytial virus |
| CXR | Chest X-ray |
| CF | Cystic fibrosis |
| PIBC | Post infectious bronchiectasis |
| BMI | Body Mass Index |
| HIV | Human Immunodeficiency Virus |
| AIDS | Acquired immunodeficiency syndrome |
| GORD | Gastroesophageal reflux disease |
| TB | Tuberculosis |
| NZ | New Zealand |
| LMIC | Low – middle Income Countries |
| WAZ | Weight for Age Z score |
| WHZ | Weight for Height Z score |

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Chapter 1

# 1.0 Introduction and review of literature

## 1.1 Background

Bronchiectasis (BC) is a chronic lung disease characterized by irreversible and progressive airway damage [1, 2]. The cardinal features of bronchiectasis include stasis of infected airway secretions, regional or diffuse airway wall dilatation, thickening and destruction with loss of airway structural integrity. There is associated prolonged neutrophilic inflammatory and secretory response within the airways that causes a recurrent chronic "wet" cough in young children and mucopurulent sputum expectoration, "productive cough" in older children. This is characterized by recurrent exacerbations. This clinical phenotype, which is the hallmark of bronchiectasis, when coupled with radiological findings of airway wall thickening and dilatation obtained with high-resolution computerized tomographic scans of the chest (HRCT scan), is the criteria for making the diagnosis of bronchiectasis [2-5].

The French physician Rene Laennec first described bronchiectasis in 1819 and recognized the pathological entities as abnormal irreversible dilated and thick-walled bronchi, resulting from a variety of pathological processes that cause destruction of the bronchial wall and its supporting tissues. Subsequently, other researchers recognized that bronchiectasis carried a poor prognosis and highlighted the importance of early diagnosis and potential for lobectomy for patient survival [2]. In the 1950s, The United Kingdom and other affluent countries reported a decline in chronic suppurative lung disease (CSLD) owing to introduction of antibiotics. The disease however remained prevalent among the poor social classes of high income countries, eventually being coined as an "orphan disease"[6].

Bronchiectasis lies at the extreme end of a spectrum of suppurative airway inflammation associated with radiological changes while an inconsequential Protracted bacterial bronchitis (PBB) lies on the other mild end without any radiological changes. Chronic suppurative lung disease (CSLD) is intermediate and has no radiological findings. The HRCT diagnostic criteria for children are different from adult criteria as the adult criteria are not sensitive to childhood bronchiectasis [7]. Various insults are responsible for the pathological changes seen in BC, including diseases that impair muco-ciliary clearance like primary ciliary dyskinesia (PCD) and cystic fibrosis (CF), disease that alter immune-responses like primary immunodeficiencies (PID) or acquired immunodeficiency syndrome (AIDS) mainly related to Human Immunodeficiency Virus (HIV) [7, 8]. Other diseases include chronic infections like tuberculosis, structural abnormalities of the airways such as bronchomalacia and congenital pulmonary airway malformations (CPAM) and diseases associated with systemic inflammation. Similarly, events that result in airway damage may cause bronchiectasis such as recurrent lower respiratory tract

illness, which are very common in early childhood, foreign body aspiration or recurrent aspiration and Eosinophilic lung disease post toxic fume inhalation (indoor or outdoor) have all been identified as causes for bronchiectasis [9]. Treatment interventions at critical stages of the spectrum have the potential to change the trajectory of the disease and halt progression.

### 1.2 Epidemiology

The burden of bronchiectasis globally reduced from the 1940s till the 1990s. This initial decline was attributed to several factors, including improved living conditions, introduction of antibiotics and immunizations, improved hygiene, nutrition, and easy access to medical facilities [2, 10]. However, it has now been recognized that there is an increase globally in prevalence, morbidity, and mortality. Affluent countries have reported increasing prevalence particularly among socially and economically disadvantaged populations [10]. The burden of disease in low - middle income countries (LMIC) is largely unknown. Despite a growing awareness among clinicians and researchers of bronchiectasis globally, robust disease burden data remains sparse in African settings. And yet this is critical information needed to guide implementation of prevention and treatment interventions.

Average annual rates of paediatric CSLD in high income European countries range from 0.2/100 000 and 2.3/100 000 in the United Kingdom (UK) and Ireland respectively [11, 12]. In other non-European affluent countries, the rate in New Zealand (NZ) is 1.5/100 000 in a population of European descent, while indigenous children in NZ had a much higher rate of 15/100 000 [13]. This was similar to the rate in the United Arab Emirates affluent indigenous population where the rate was 13.3/100 000 [14]. Other countries that have reported high rates in indigenous populations include the pacific island population [15], Australia [16-18], Alaska[19, 20] and Canada [21] where the prevalence ranges between 147 to 200/100 000. Poor living conditions associated with poverty, overcrowded households, poor access to medical services, exposure to indoor (cooking fumes and tobacco smoke) and outdoor pollution (campfires, traffic, industrial pollutants) and high unemployment characterize these indigenous populations [2, 10]. Also common to these disadvantaged populations is the high prevalence of early and recurrent childhood pneumonias [16, 17] in contrast to affluent countries where non-infectious causes are common [2, 22, 23].

The incidence of bronchiectasis in children in 2003 in Auckland NZ was reported as 24/100 000 for Maori population while European population was lower at 4/100 000 [24]. The rate of bronchiectasis hospitalizations between 2003-2005 was reported as 3.6 times the rate for the non-Maori population, indicating a higher incidence rate in indigenous populations compared to European populations [25]. These rates are comparable to adult data were the USA reported an incidence of 4.2/100 000 for 18–34-year-olds and higher (272/100 000) in older patients [26].

The burden of paediatric bronchiectasis in LMIC, particularly from sub-Saharan Africa, is mostly unknown. A lone study from Nigeria reported that 14% (70/1150) of patients consecutively admitted with respiratory or cardiovascular disease to hospital between 1975 and 1979 had CSLD [27]. Reasons for this paucity of data from African settings include complex diagnostic protocols that require HRCT, which is not commonly accessible in many LMIC of sub-Saharan Africa. Further, physicians in these settings are unable to fully evaluate patients with chronic respiratory disease due to poor laboratory and radiological diagnostic capacity. Consequently, patients are assigned other diagnoses such as difficult asthma or chronic obstructive pulmonary disease, thus missing bronchiectasis diagnosis in childhood and missing the opportunity to prevent disease [28-30].

Poor outcomes associated with bronchiectasis has been reported from low income countries where 22% of patients had respiratory failure in a 6.6 year follow up in a Tunisian study [31]. Roberts et al, reported a mortality of 12 deaths in children below 14 years between 2001 and 2007 in England and Wales while Munro et al reported 6/91 children died in a NZ clinic between 1991 and 2006 [32, 33]. Early diagnosis and intervention prevent poor outcomes and mortality [2, 10, 30].

### 1.3 Pathogenesis and Aetiology

There is still more to understand about the pathogenesis of bronchiectasis. It is however understood and accepted that bronchiectasis results from a cycle of phases of infection, chronic inflammation, impaired mucociliary clearance and mucus hypersecretion, microbial colonization and bronchial dilatation and airway architecture destruction, which in turn perpetuates chronic infection. This has been termed the “vicious cycle” of bronchiectasis or more recently, the “vicious vortex” of bronchiectasis [34].

A complex interplay of host immune response, early respiratory infections, previous lung injury, socioeconomic determinants, congenital airway lesions, underlying disease processes, pathogenic factors and environment determinants play a role in the pathophysiology underlying bronchiectasis [20]. Antecedents for the initial infections may include congenital airway malformations, cystic fibrosis, immune deficiencies, and aspiration syndromes. The severity of disease is influenced by many factors: colonizing organism factors, host genetic factors and environmental factors.

Common infective organisms include gram negative (e.g *Haemophilus influenza, Pseudomonas aeruginosa, Moraxella catarrhalis*), gram positive (*Streptococcus pneumoniae, Staphylococcus aureus), tuberculosis, fungal, viruses (coronavirus, Rhinovirus, influenza* A and B). Masekela et al reported that the commonest organisms among children with HIV related bronchiectasis at a tertiary hospital in South Africa was *H. influenzae* and *Parainfluenza* in 49% of sputum cultures

and 1% *Staphylococcus aureus* [35]. On the other hand, Verwey et al found *H. influenzae* was the commonest bacterium ( 36%) followed by *streptococcus pneumoniae* (12.6%) with no significant difference between HIV infected and uninfected patients in type of pathogen isolated [36].

Previous acute lower respiratory infections (ALRIs) are an important risk factor in children for developing bronchiectasis and abnormalities in lung function that can extend into adulthood [37, 38]. Single severe ALRIs due to tuberculosis, adenovirus and pertussis have been linked to development of bronchiectasis in less affluent populations [39, 40]. It has also been shown that children who have been previously admitted for ALRIs with focal or diffuse alveolar changes are at increased risk of bronchiectasis, with recurrent pneumonia hospitalization also being associated with development of bronchiectasis later in childhood [41].

Bronchiectasis is mostly classified using Reid's subtypes, which include cylindrical, varicose and cystic types, which were based on bronchographic findings. Plain chest radiography is known to be normal in patients with bronchiectasis and therefore insensitive as a diagnostic tool. As such, HRCT is the gold standard for making a diagnosis of bronchiectasis [10]. HRCT scoring systems describe cylindrical and saccular changes as markers of disease severity and saccular and cystic changes reflect more advanced severe and irreversible disease. Macroscopically, the airways are tortuous and dilated and this extends to the pleural surface. As the disease advances, destruction of the airway muscle, elastic and cartilage ensues and renders the airways thin and saccular, and they fill with mucus. These changes are accompanied by vascular changes that may cause hemoptysis due to development of large bronchopulmonary anastomosis. In severe cases, pulmonary hypertension and cor pulmonale may develop [10].

### 1.4 Clinical features

Clinical features differ depending on the severity of disease and vary in different reports. Chronic wet or productive cough is the hallmark of bronchiectasis in children and is the earliest and most important symptom to investigate [2, 10, 42]. Wet cough is also an important symptom in recognizing exacerbations in patients with bronchiectasis. Exacerbations are an important part of bronchiectasis in children as they are associated with poor quality of life, decline in lung function and increased use of health care services and cost, and may be used to evaluate the efficacy of interventions [43]. In older children, the cough is productive of purulent or mucopurulent sputum while younger children may not expectorate. LMIC report high rates of cough, 75% in indigenous Alaskan cohorts while 100% cough rate was reported in Australia, an affluent setting [16, 19]. Poor awareness and under appreciating the significance of cough has the potential to delay diagnosis and management, which impacts future lung function and leads to poor outcomes.

Wheezing is common in children with bronchiectasis which has been reported to be 20-66% in LMIC and 10% in UK children [2]. Indigenous children from Alaska reported a high percentage of 41% wheezing compared to indigenous Australian children at 7% and 17 % for pacific island children. The risk factors for wheezing phenotypes needs to be explored further [2, 19, 44-46].

Other clinical features have varied frequency in various reports and include hemoptysis, failure to thrive, finger clubbing, recurrent chest infections, crackles and hyperinflation. Hemoptysis is less common in children compared to adults and may be a sign of severe disease together with reduced oxygen saturations, cor pulmonale, chest wall deformity and growth failure [1, 2, 10].

Pulmonary function tests are frequently used as an objective tool for assessing extent of bronchiectasis and reflects severity of disease [2, 10]. Different studies have reported varied findings, with lower predicted FEV1 among children from LMIC compared to children from high income countries [2]. Spirometry is insensitive in detecting early signs of lung damage in children. Obstructive changes may be observed in the early stages of bronchiectasis with mixed obstructive and restrictive pattern in the later stages [10]. Lung clearance index in children with cystic fibrosis bronchiectasis shows that early ventilation inhomogeneity in peripheral airways is detected much earlier than spirometry. Data from bronchiectasis unrelated to CF in children is lacking [10].

The age of diagnosis of bronchiectasis varies in different reports, with NZ reporting 9 to 10 years at diagnosis while other affluent countries report a median of 4-5 years [2]. Older age at diagnosis has been associated with more advanced disease [2].

### 1.5 Management

Early diagnosis of bronchiectasis facilitates early initiation of treatment and arrests progression of disease and preserves lung capacity [28, 47, 48]. There is recent suggestion that mild radiological findings of bronchiectasis on HRCT (cylindrical) has shown some resolution if diagnosed and treated early [49, 50]. Treatment protocols used in children with CF bronchiectasis have been extrapolated to management of children with bronchiectasis unrelated to CF. These protocols include aggressive management of infections with antibiotics, use of regular airway clearance methods, optimizing nutrition, monitoring lung function, minimizing acute exacerbations, sputum surveillance and immunizations. These interventions require a multidisciplinary approach that includes nursing, physiotherapy, nutritionist, and social worker to optimize care [9, 51, 52]. Recently published bronchiectasis guidelines highlighted the need for further research in childhood management of bronchiectasis not related to cystic fibrosis [9, 43, 52].

### 1.6 Prevention

Prevention of bronchiectasis requires a multidisciplinary approach that optimizes screening of children among high-risk individuals, early diagnosis, and treatment. Childhood immunizations and breastfeeding are known to prevent early and severe childhood pneumonia that have the potential to complicate into bronchiectasis. Screening, identifying, and treating primary immunodeficiency disorders early prevents the development of bronchiectasis in at risk children. Exposure to environmental pollutants, both indoor and outdoor (tobacco, biomass fuels and camp fires), is known to cause bronchiectasis [9, 43]. Other important well recognized modalities of preventing bronchiectasis are improving childhood nutrition, hygiene and sanitation, improvement in housing, reduction in household crowding and improving access to medical services [10].

South Africa, being a LMIC in sub-Saharan Africa, has a high prevalence of risk factors associated with bronchiectasis, including high burden of HIV infection, tuberculosis, childhood pneumonia, poor housing and overcrowding in poor communities [35]. There is therefore urgent need to understand the epidemiology and clinical spectrum of bronchiectasis. This understanding will help inform interventions with the potential to prevent bronchiectasis and prevent poor outcomes. The current study will provide baseline data from a LMIC setting where there is a clear knowledge gap. It will also provide guidance for further larger studies in the region, including the initiation of a registry of children with bronchiectasis in South Africa.

## 2.0 Overall Objectives

The overall aim of this research is to describe the burden of disease, aetiology, and clinical spectrum of bronchiectasis (excluding cystic fibrosis) in children attending a tertiary paediatric Respiratory service at Red cross war memorial children's hospital (RCWMCH) in Cape Town, South Africa

### 2.1 Specific Objectives

1. To investigate the burden and aetiology of bronchiectasis amongst children aged 3 months to 15 years attending the Respiratory clinic at RCWMCH from January to December 2019

2. To describe the clinical symptoms, signs, and disease severity of bronchiectasis amongst children aged 3 months to 15 years attending the respiratory specialist clinic at RCWMCH from January 2019 to December 2020

## 3.0 Methodology

### 3.1 Type of study and inclusion criteria

This was a retrospective cross-sectional study undertaken at RCWMCH in Cape Town, South Africa. A chart review of children diagnosed with bronchiectasis attending the respiratory clinic at RCWMCH between January 2019 and December 2019 was conducted. Children were included if the clinical records indicated that they had a diagnosis of bronchiectasis based on history of a recurrent wet cough (> 3 episodes/year) or persistent (> 4 weeks) productive or wet cough, a clinical phenotype characterized by any of the following; exertion dyspnea, airway hyper responsiveness, recurrent chest infections, growth failure, finger clubbing and chest deformity, had characteristic radiographic features of bronchiectasis on chest X-ray or chest computer tomography scan (CT scan) reported by the hospital radiologist and they were in the age group between 3 months and 15 years and attended the clinic between January 2019 and December 2019.

## 4.0 Ethical Approval

Ethical approval for the study was given by the Human Research Ethics Committee, University of Cape Town in 2020 (HREC REF: 179/2020) and the Red Cross War Memorial Children's Hospital research review committee (REF: RXH: RCC 226). Waiver of consent was granted for clinical chart review of the patients.

## 5.0 Author Guidelines

European Respiratory Journal has been chosen for publication of this study. This is a monthly peer reviewed medical journal covering respirology and is the official journal of the European Respiratory society under ISSN 0903-1936 (print): 1399-3003 (web).

## 6.0 Manuscript Guidelines for original research articles

The manuscript must be written in UK English and the word count should not exceed 3000 with no more than 8 tables/figures. The manuscript must include Title page, Take home message, abstract, discussion and references.

The full details of the author guidelines are in Appendix B

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Chapter 2

Publication ready manuscript

Title page

**Bronchiectasis in african children: prevalence, aetiology and clinical spectrum at a paediatric tertiary hospital in Cape Town, South Africa**

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**Take Home message**

Lack of data on bronchiectasis in African settings prompted us to investigate disease burden, causes and clinical spectrum in African children in South Africa at a tertiary Hospital in Cape Town. We collected data from the clinical files of children attending the respiratory clinic between January to December 2019.
We found 17.2% disease burden with young average age (34 months) at diagnosis; 27.6% were living with HIV. Post pneumonia causes predominate, with tuberculosis being commonest among children living with HIV. We highlight the importance of interventions that prevent pneumonia in children, especially tuberculosis in children living with HIV.

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## ABSTRACT

Childhood bronchiectasis is a common cause of chronic lung disease globally, particularly in lower-middle-income countries (LMIC). Data from LMIC is lacking. We aimed to describe the disease burden, aetiology, and clinical spectrum of bronchiectasis in children attending a tertiary hospital in Cape Town, South Africa.

### Methods

Data was collected by chart review of all patients 3 months to 15 years attending the respiratory clinic at Red Cross War Memorial Children's Hospital between January – December 2019. We included children who had a diagnosis of bronchiectasis based on history of a recurrent (> 3 episodes/year) or persistent (> 4 weeks) wet cough and a clinical phenotype characterized by any of the following: exertion dyspnea, recurrent chest infections, growth failure, finger clubbing and chest deformity associated with radiographic features of bronchiectasis on chest X-ray or HRCT reported by a paediatric radiologist. Patients with cystic fibrosis were excluded.

### Results

Of 337 children seen during the study period, 58 (17.2%) had bronchiectasis that was diagnosed at a mean age of 34 months (SD 26). There were 32 (55.0%) female participants. The commonest causes of bronchiectasis were post-infectious (25, 43.1%), and underlying immunodeficiencies (19, 32.8%) including 16/58 (27.6%) who were HIV-infected and 3 (5.1 %) with primary immunodeficiency. Other causes included aspiration syndrome (8, 13.8 %) and anatomical abnormalities (4, 6.9%). Of the participants with post infectious bronchiectasis, tuberculosis was the commonest organism that was isolated (16, 64.0%) and commonest in children living with HIV (11/16, 68.8%). Cough was common (48, 82.8%) with wet cough being predominant (41, 85.4%), course crepitations accounted for 37 (63.8%), hyperinflation 24 (41.4%) finger clubbing 21 (36.2%), wheeze 16 (29.3%) and exertional dyspnea in 7 (12.0%).

**Conclusion:** Bronchiectasis is a common cause of chronic lung disease in South African children mostly resulting from previous pneumonias, with tuberculosis being the commonest infective cause. The importance of identifying underlying treatable causes is highlighted.

## Introduction

Bronchiectasis is a chronic lung disease characterized by irreversible airway damage [1]. The cardinal features of bronchiectasis include stasis of infected airway secretions, regional or diffuse airway wall dilation, thickening and destruction with loss of structural integrity. The associated prolonged neutrophilic inflammatory and secretory response within the airways cause a chronic or recurrent "wet" cough in young children and mucopurulent sputum expectoration in older children characterized by recurrent exacerbations. This clinical phenotype, coupled with radiological findings of airway wall thickening and dilatation obtained with high-resolution computerized tomographic scans of the chest (HRCT) are the criteria for making a diagnosis of bronchiectasis [3-5]

Bronchiectasis lies at the end of a continuum of suppurative airway inflammation that ranges from an inconsequential protracted bacterial bronchitis to the chronic suppuration that leads to irreversible airway damage and results from different disease processes or insults [7, 10]. These include diseases that impair muco-ciliary clearance (e.g., primary ciliary dyskinesia (PCD) and cystic fibrosis (CF)), alter immune-responses (e.g., primary or acquired immunodeficiency, chronic infections), structural abnormalities of the airways (e.g., bronchomalacia, trachea-esophageal fistula, bronchomegaly) or disease associated with systemic inflammation. Similarly, events that result in chronic inflammation and/or airway damage, such as recurrent lower respiratory tract illness, foreign body aspiration or recurrent aspiration, may cause bronchiectasis [9].

The global burden of bronchiectasis has declined over the past decades and is attributed to improved living conditions and improved access to antibiotics and medical facilities [10]. However, it has now been recognized that there is a global increase in prevalence of bronchiectasis with associated morbidity and mortality, especially in children living with social deprivation [2, 16, 19]. The global prevalence of bronchiectasis is reported to be 14.7/1000 in Australia 's northern territory (children < 15 years), while Alaska reports a prevalence of 14-20/1000 births in Yukon Kuskokwim Delta. On the other hand, New Zealand reports a lower prevalence of 0.7/1000 in Maori children < 15 years and Pacific Island children of 1.6/1000 [19] The true global paediatric prevalence is difficult to determine due to diagnostic criteria needing HRCT, which is not easily accessible in low and low-middle income settings. Hence there remains a paucity of data from these settings, and minimal data from Africa, despite a high burden of paediatric chronic lung disease [2, 28].

Current evidence suggests that early diagnosis and treatment improves outcomes. However, delayed diagnosis remains common and mainly arises from low awareness of bronchiectasis among clinicians and limited access to diagnostic tools [53, 54]. Further, there is evidence that the majority of adult disease has its origins in childhood [28, 29]. It is hence important that we

improve our knowledge of bronchiectasis in African children, where risk factors for disease are common and may differ from other settings. Further, this would facilitate development of effective prevention, diagnostic, and management strategies with the potential to improve the trajectory of the disease.

The aim of this study was to describe the burden of disease, aetiology, and clinical spectrum of bronchiectasis (excluding cystic fibrosis) in children attending a tertiary paediatric respiratory service at red cross war memorial children's hospital (RCWMCH) in Cape Town, South Africa.

## Methodology

### Study design and inclusion criteria

This was a retrospective cross-sectional study undertaken at RCWMCH, Cape Town, South Africa. A chart review of children diagnosed with bronchiectasis attending the respiratory clinic at RCWMCH between January and December 2019 was conducted. Children between 3 months and 15 years who attended the clinic between this period were included if the clinical records indicated that they had a diagnosis of bronchiectasis based on: 1. History of a recurrent (> 3 episodes/year) or persistent (> 4 weeks) productive or wet cough, 2. A clinical phenotype characterized by any of ; exertion dyspnea, recurrent chest infections, growth failure, finger clubbing and chest deformity) and 3. Characteristic radiographic features of bronchiectasis on plain chest radiography or HRCT reported by a paediatric radiologist. Patients with bronchiectasis related to cystic fibrosis are followed up in a dedicated cystic fibrosis multidisciplinary clinic and were not included in this study.

### Ethics Approval

Ethical approval and authority to waiver informed consent for the study was granted by the Human Research Ethics Committee, University of Cape Town (HREC 179-2020).

### Data Collection

Data was collected from the patient clinic files using the pre-designed study case report form (CRF), Appendix A in supplemental material. Patient demographic and nutritional status details (using WHO reference values), past medical and family history, clinical details at diagnosis, aetiology of bronchiectasis and current clinical details were collected as documented in the clinical notes during admission to hospital and/or during follow up in clinic.

Participant's current clinical symptoms and signs were collected from the last visit in 2019 and a review of all the clinic visits during 2019. Radiology and laboratory (including histology) results were recorded from the radiology online portal and National Health Laboratory Service system

respectively. Plain Chest radiographs and HRCT scans were reported by a paediatric radiologist and categorized as normal, diffuse or focal disease; dilated and thick airway walls, non-tapering airways, presence of tram tracks and 'signet ring' sign. Lung function was measured with spirometry and bronchodilator response testing. Testing was done using a CareFusion spirometer (MS Pneumoscope, Jaeger-Carefusion, Germany) by a trained respiratory technologist and following international guidelines [55]. The first ever spirometry result obtained since admission to respiratory clinic and last spirometry results obtained in 2019 were collected. Measures included the forced expiratory volume in one second ($FEV_1$), forced vital capacity (FVC) and the $FEV_1$/FVC ratio. Bronchodilator response (BDR) was measured after repeating the test 15min after 400mcg salbutamol was administered via spacer. The Quanjer GLI 2012 reference equation was used to interpret tests [56]. In patients who had a bronchoscopy done, findings were collected.

**Data Analysis**

Data was entered on a Redcap database from the CRF. Descriptive statistics were used to describe characteristics of the study population, clinical signs, symptoms and disease severity. For normally distributed data, mean and standard deviation (SD) were used. The burden of bronchiectasis among the study population was expressed as count (percent) (Proportion of patients with bronchiectasis against total patients in 2019). Summary proportions were used to express the aetiology of bronchiectasis.

**Results**

**Disease burden**

There was a total of 627 clinic attendances (including repeat visits) for the period January 2019 to December 2019. A total of 337 patients attended clinic. Of the patients, a total of 58 patients met the inclusion criteria for the study, giving a clinic prevalence for bronchiectasis of 17.2 %. The diagnosis of bronchiectasis was based on chest X-ray for 30 (53.4%) and on HRCT in 28 (46.6%) participants. Figure 1

**Demographic and Clinical characteristics**

Cohort demographics are presented in Table 1. The mean (SD) age at enrolment was 92.2 (41.0) months. Most patients, 50 (86.0%), were older than 5 years and 32 (55%) were female. The mean (SD) age at diagnosis was 34.2 (26.3) months with over a third, 21 (36%), diagnosed before 24 months. Further, mean age at diagnosis for males was 34.7 (31.6) and 33.9 (22.8) for females. Nutritional status was normal for most, with mean (SD) weight for height z-score (WFZ) of 0.0 (1.6). The mean (SD) height for age z-score (HAZ) was 1.2 (1.6). None were stunted, underweight nor obese. The gestational age at birth ranged from 32 to 40 weeks, mean

(SD) 37.5 (1.3); only 8 (13.8%) were pre-term and none early preterm (<32 weeks). Sixteen (27.6%) were Human Immunodeficiency virus (HIV) infected and 6 (10.3%) were HIV-exposed but uninfected (HEU). All children had a history of at least one previous lower respiratory tract infection (LRTI), with an average of 2 (SD 1.2) events, including an average of 2 (SD 0.9) hospital admissions ever for LRTI per child. Diagnostic work up included bronchoscopies in 34 (58.6%) children, 3 (5.2%) lung biopsies and 23 (39.7%) upper gastrointestinal tract scintigraphy (milk scan).

**Bronchiectasis Aetiology**

The commonest cause of bronchiectasis in our cohort was post infection bronchiectasis, 25 (43.1%) children. Nineteen (32.8%) children had underlying immunodeficiencies; 16/19 (84.2%) had HIV disease and 3/19 (15.8%) had primary immunodeficiency (PID). Other causes included gastroesophageal reflux disease (GORD) and aspiration syndrome in 8 (13.8%), airway anatomical abnormalities in 4 (6.9%) and 2 (3.4%) participants had bronchiectasis of unknown cause.

Amongst the children with post-infectious bronchiectasis the commonest responsible organism was mycobacterium tuberculosis (TB), 16/25 (64.0%), followed by adenovirus, 8/24 (37.5%). Eleven of 16 (68.8%) HIV-infected children had post TB bronchiectasis and 2 had post-adenovirus bronchiectasis. Microbiological co-infection was common among all participants as shown in table 3.

**Clinical Spectrum, imaging, and lung function**

Children had an average (SD) of 2 (1.1) clinic visits during the year with nearly a quarter (22%) of children having more than two visits. The commonest reported symptom was cough in 48/58 (82.8%) participants, of which 42 (87.5%) described cough as wet, 4 (8.3%) both wet and dry cough and 2 (4.1%) dry cough, 19 (39.6%) reported cough multiple times daily, while 16 (33.3%) reported having cough only when sick. Continuous sputum production was reported by 20 (41.7%), 13 (27.1%) reported sputum production only when sick and 12 (25.0%) reported to cough seldomly. Ten (17.2%) participants did not have cough during 2019. Other reported symptoms were exertional dyspnea in 7/58 (12.1%), wheeze in 17/58 (29.3%), of which over half, 9/17 (52.9%), wheezed multiple times daily. Twenty-three (39.7%) participants had one exacerbation in 2019 while 12 (20.6%) had 2 or more exacerbations. Twenty-three (39.7%) participants had no exacerbations in 2019. Females were more likely to have had more than one exacerbation compared to male children, (p=0.002). Only 2 (3.4%) participants were on home oxygen during review period, both were on oxygen in the initial 6 months after diagnosis and were weaned off by end of 2019. Thirty-six (62.1%) children had finger clubbing; 37(64.0%) had coarse crepitations on auscultation.

Baseline chest X-ray at admission to respiratory clinic showed diffuse disease for 48 (82.8%) and focal disease in 10 (17.2%). Most children, 54 (93.1%), had sputum surveillance culture results in 2019. Of these 38 (70.4%) grew normal respiratory flora, 2 (3.7%) cultured MTB, and 7 (13.0 %) had no growth. Other organisms isolated, representing 1(1.9%) participant each, included *Bordetella pertussis*, *Parainfluenza, Moraxella catarrhalis*, *Staphylococcus aureus, Pseudomonas aerugin*osa and Candida species and a mixed growth of *Pseudomonas aeruginosa and M. catarrhalis*. The predominant virus isolated was *A*denovirus in 3 (9.4%) and RSV in 2 (6.2%) of participants. Other viruses isolated as mixed growths are shown in table 5.

Thirty-three (56.9%) children had spirometry results of first ever tests after enrolment and last test done in 2019. Average (SD) time interval between tests was 60 (3.2) months. This included the $FEV_1$, FVC and the ratio of $FEV_1$/FVC, the results of the mean (SD) z-score are tabulated in table 6. The mean (SD) z-score for $FEV_1$ was -4.3(1.1) at enrolment and -3.9(1.0) at the last test in 2019 with no statistically significant difference (p=0.0003) using the t-test to compare the two variables.

**Discussion**

Bronchiectasis is an important cause of chronic lung disease among South African children, representing 17.2% of all patients attending a tertiary respiratory clinic. The commonest cause of bronchiectasis was post infectious, though all children had a history of recurrent lower respiratory tract infections. The commonest cause of LRTI was TB and Adenovirus, which differed by HIV status. This highlights the importance of strengthening diagnostic pathways for children at risk of bronchiectasis and pneumonia preventive strategies for all children. Chronic respiratory symptoms were common with mean lung function in the cohort severely impaired over the study period. This study adds to the body of knowledge on bronchiectasis in African children.

Bronchiectasis was common in our tertiary respiratory clinic. A study in Zimbabwe had a higher prevalence of more than 40% among adolescents with delayed diagnosis of vertically acquired HIV infection, though this was characteristically described as severe hypoxic lung disease [57]. Studies in high income countries found a prevalence ranging from 0.2 – 2.3/100 000 in European countries and 1.5/100 000 in New Zealand people of European descent, prevalence in disadvantaged and indigenous communities in these same settings found a higher prevalence of 15/100 000 in New Zealand and 17.8 – 18.3/100 000 population in pacific islanders.[2] The high burden in our clinic population reflects both the selected population of children with CLD and the setting of high-risk factors for bronchiectasis, notably TB, HIV and high infective exposure. Community prevalence data from South Africa is needed.

Although the commonest cause of bronchiectasis in our cohort was attributed to post infectious causes, nearly a quarter of our children had immune deficiencies, mainly arising from perinatally acquired HIV. These children all had a history of recurrent or severe LRTI. Tuberculosis is endemic in sub-Saharan Africa and not surprising that it was the commonest cause identified in children living with HIV (68.8%) and 19.3% in HIV uninfected children. Adenovirus has been found to cause long-term sequalae, including bronchiectasis, following respiratory infections as a single infection or co-infection with other organisms [58, 59]. This is similar to our findings where adenovirus was isolated as single organism as well as a co-infection The commonest cause of bronchiectasis among indigenous poor communities in Australia was reported to be post infection / idiopathic (94.5%) [60], similar to our results although our cohort was hospital based. Other common causes like GORD, PID and congenital or acquired airway anatomical abnormalities are antecedent to recurrent respiratory infections which may further result in bronchiectasis. Primary Ciliary Dyskinesias (PCD) and PID have been recognized to be common among societies with high frequency of consanguinity like in Turkey [61], while the incidence of cystic fibrosis (CF), and PCD are unknown in LMIC due to limited diagnostic capacity[1, 60] . Determination of the aetiology of bronchiectasis is important and key to successful management of the disease.

Our children were younger at diagnosis (mean age 34 months) compared to older children at 9-10 years in New Zealand, which was characterized by more advanced disease [10]. Diagnosis of bronchiectasis in infancy has been associated with congenital lung malformation and other genetic diseases like PCD [10]. The diagnosis of bronchiectasis in our cohort was made early and this demonstrates that children who are at risk of bronchiectasis may present early and should be screened for bronchiectasis.

Similar to previous studies, chronic wet cough was the most common symptom [1]. Other researchers have reported 28-100% chronic wet cough in children from LMIC [1]. Cough is the earliest and most important symptom to recognize and investigate in children with suspected bronchiectasis [2]. Not recognizing this causes delay in diagnosis and treatment and has negative impact on prognosis, increase spending on national health budgets and family expenditure. Increasing productive cough is a sign of exacerbation and requires escalation of management interventions. Therefore, strengthening prevention, early diagnosis and care has the potential to mitigate these untoward effects.

Wheeze was present in a quarter (27.6%) of our cohort, which was similar to findings in Tunisia (20%). United Kingdom reported a lower prevalence of wheezing (10%) and Alaskan children had high prevalence of wheezing (41%) which was attributed to RSV hospitalization [19]. In our cohort, RSV was isolated as a co-infection in 2 HIV-uninfected children. Finding of wheezing is variable among different studies and needs further evaluation to determinate the true prevalence and the underlying risks.

Features of severe bronchiectasis in children may include clinical features like exercise intolerance, frequent exacerbations, hemoptysis, frequent attendances at clinics, failure to thrive, reduced lung function, use of home oxygen and presence of finger clubbing [1, 60, 62]. These features were not predominant in our cohort. Early diagnosis in our cohort and access to appropriate care may be responsible for this.

Diffuse or multilobe disease on the baseline chest Xray was predominant compared to focal disease, which is sometimes used as a marker of disease severity. Focal disease maybe associated with foreign body aspiration though our cohort did not have that history. Despite this preponderance of diffuse disease on the baseline chest Xray, our cohort did not have predominant severe disease. Chest Xray changes in our patients were persistent and thus HRCT was not offered. In addition, it is not always feasible to recommend HRCT for all patients to diagnose bronchiectasis in LMIC as per guidelines from high income countries. This may have limited our ability to diagnose all patients with bronchiectasis. We however highlight the need for earlier diagnosis to prevent this extent of disease, and HRCT plays an important role in detection of early disease and can facilitate targeted investigations and treatment.

Sputum surveillance results had few children with *H. influenzae or H. parainfluenza*, which were the predominant organisms in a developing world setting in children living with HIV [63]. *H. influenzae* accounted for 47% in children having exacerbations in Australia [60]. TB was isolated on surveillance sputum done in 2019, being endemic in our setting and can easily cause opportunistic infections in bronchiectasis patients. Our cohort are on prophylactic azithromycin, which may be responsible for low bacterial load in sputum [2, 64]. Anna brooke-Hollidge et al reported that low pathogen load in sputum was associated with the mildest form of disease.[65]

This is the first study to describe the aetiology and clinical spectrum of bronchiectasis in South African children attending a general respiratory clinic. The strength included access to comprehensive clinical information and investigations. Limitations of the study include being a retrospective study, we relied on data from clinical records. Although these were available for all children and had been collected by the same team of experienced pulmonologists, there may be reporting bias. The description of more severe disease in this cohort is likely a selection bias of children referred to a specialist respiratory clinic. Further, the research was conducted in a tertiary center and so unlikely to reflect the general population. Further data is needed to describe disease burden, aetiology, and clinical spectrum at community level.

## Conclusion

Bronchiectasis is common in our tertiary respiratory setting and an important cause of lung morbidity in children. Post infectious causes are the most predominant due to high burden of

early respiratory childhood infections in this setting. Post-TB bronchiectasis in children, including those living with HIV, is an important cause in TB-endemic settings and is the leading cause of bronchiectasis in children living with HIV. Prevention, early diagnosis, and management of TB in children can prevent development of bronchiectasis. Clinical features of bronchiectasis vary depending on extent of disease. Chronic wet cough remains the hallmark clinical feature of bronchiectasis and any such cough in children should be evaluated further to facilitate early diagnosis and early intervention.

**Tables and figures**

**Figure 1**
**Burden of Disease Flowchart**

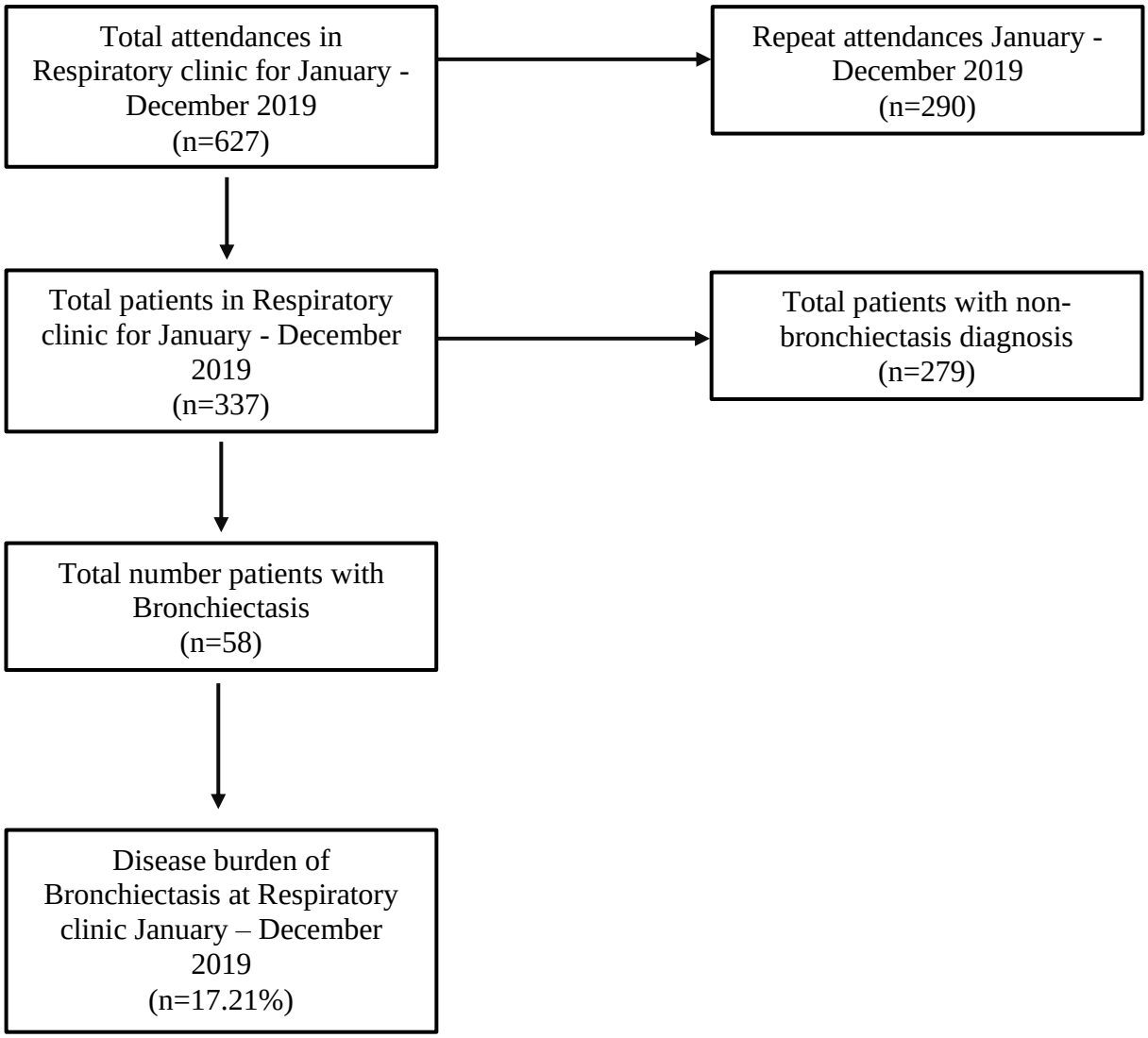


**Figure 1***: This figure shows the protocol that was used to determine the disease burden in the respiratory clinic. A total of 337 patients attended the clinic between January and December 2019 and 58 had bronchiectasis, being 17.2% disease burden.*

**Table 1**
**Demographic and Anthropometric Data of cohort (n=58)**

| **Patient characteristic** | |
|---|---|
| **Sex (number, %)** | |
| Female | 32 (55.2) |
| Male | 26 (44.8) |
| **Age (months) at enrolment (Mean, SD)** | 92.2 (41.0) |
| Males | 95.5 (47.9) |
| females | 89.3 (34.7) |
| **Age (months) at diagnosis (Mean, SD)** | 34.2 (26.3) |
| Males | 34.7 (31.6) |
| Females | 33.9 (22.8) |
| **HIV status (number, %)** | |
| HIV unexposed and uninfected | 36 (62.0) |
| Positive | 16 (28.0) |
| HEU | 6 (10.0) |
| **Gestation age at birth in weeks** (mean SD) | 37.5 (1.3) |
| Term (≥37 weeks) | 53 (91.4) |
| Preterm (Below 37 weeks) | 8 (13.8) |
| Received Oxygen therapy at birth (number, %) | 5 (9) |
| WHZ*, Mean (SD) | 0.0 (1.6) |
| HAZ*, Mean (SD) | 1.2 (1.6) |
| Number of chest infections ever, mean (SD) | 2 (1.2) |
| Number of admissions ever, mean (SD) | 2 (0.9) |
| Radiology Basis for bronchiectasis diagnosis (number, %) | |
| Chest Xray | 30 (51.7) |
| HRCT | 28 (48.3) |

HIV: Human immunodeficiency virus, HEU: HIV Exposed Uninfected, WHZ: weight for height z-score, HAZ: height for age z score, HRCT: high resolution computer tomography.
*calculated from WHO percentile charts [66]

**Table 2**
**Causes of Bronchiectasis**

| Cause of bronchiectasis | Number (%) |
|---|---|
| 1. Post infection bronchiectasis | 25 (43.1) |
| 2. Immunodeficiency | 19 (32.8) |
| i) HIV | 16 (84.2) |
| ii) Primary immune deficiency | 3 (15.8) |
| a. Agammaglobulinemia | 1 (33.3) |
| b. Immunoglobulin A deficiency | 2 (66.7) |
| 3. GORD and aspiration | 8 (13.8) |
| 4. Airway anatomy abnormalities: | 4 (6.9) |
| a. Right sided distal tracheobronchomalacia | 1 (1.7) |
| b. Right upper lobe branching abnormality | 1 (1.7) |
| c. CPAM type 1 | 1 (1.7) |
| d. Tracheoesophageal fistula Repair | 1 (1.7) |
| 5. Bronchiectasis of unknown cause | 2 (3.4) |

GORD: Gastroesophageal reflux disease, CPAM: Congenital pulmonary adenomatoid malformation

**Table 3**
**Causative organisms by HIV status**

| Causative Organisms by HIV status | Number (%) |
|---|---|
| 1. HIV infected (n=16)<br>a. Mycobacterium tuberculosis<br>b. Adenovirus<br>c. Co-infection | <br>11 (68.8)<br>1 (6.2)<br>4 (25.0) |
| 2. HIV exposed uninfected<br>a. Mycobacterium Tuberculosis<br>b. Adenovirus<br>c. Co-infection | <br>0 (0.0)<br>1 (16.7)<br>5 (83.3) |
| 3. No HIV infection<br>a. Mycobacterium Tuberculosis<br>b. Adenovirus<br>c. Co-infection | <br>5 (19.3)<br>7 (22.6)<br>25 (80.6) |

Co-infection organisms: *Adenovirus, Human meta-pneumo virus, Human papilloma virus, Respiratory syncytial virus, Enterovirus, Moraxella catarrhalis, Haemophilus Influenza, Corona Virus, Human rhino virus*

**Table 4**
**Clinical Spectrum, laboratory, and radiological results (n=58)**

| Clinical feature | Number (%) |
|---|---|
| **Cough** | 48 (82.8) |
| **Cough character (n=48)** | |
| Wet | 42(72.4) |
| Dry | 2(3.4)) |
| Both wet and Dry | 4(6.9) |
| **Cough Frequency (n=48)** | |
| Multiple times / day | 19 (39.6) |
| Only when sick | 16 (33.3) |
| Seldom | 12 (25.0) |
| Once / day | 1 (2.1) |
| **Sputum production (n=48)** | |
| Continuously | 20 (41.7) |
| Only when sick | 13 (27.1) |
| Seldom | 12 (25.0) |
| none | 3 (6.2) |
| **Wheeze ever** | 16 (27.6) |
| **Exertional dyspnea (self reported)** | 7 (12.1) |
| **Crepitations** | 37 (63.8) |
| **Number of exacerbations in 2019** | |
| One | 23 (39.7) |
| Two | 10 (17.2) |
| 3 and more | 2 (3.4) |
| No exacerbations in 2019 | 23 (39.7) |
| **Hyperinflation of the lungs** | 24 (41.4) |
| **Home oxygen use** | 2 (3.4) |
| **Finger clubbing** | 21 (36.2) |
| **Baseline chest x-ray (n= 58)** | |
| Focal disease | 11 (19.0) |
| Diffuse disease | 47 (81.0) |
| ***Sputum Culture Results (last sputum surveillance 2019, n= 54, 93%)*** | |
| Normal respiratory flora | 38 (70.4) |
| No growth | 7 (13.0) |
| *Mycobacterium Tuberculosis* | 2 (3.7) |
| *Bordetella pertussis* | 1 (1.9) |

| | |
|---|---|
| *Candida species* | 1 (1.9) |
| *Hemophilus influenzae* | 1 (1.9) |
| *Moraxella catarrhalis* | 1 (1.9) |
| *Staphylococcus aureus* | 1 (1.9) |
| *Pseudomonas aeruginosa* | 1 (1.9) |
| *Pseudomonas aeruginosa mixed with M. catarrhalis* | 1 (1.9) |
| *No sputum submitted in 2019* | 4 (6.9) |
| **Viral panel (n=32)** | |
| *Adenovirus* | 3 (9.4) |
| *Bocavirus* | 1 (3.1) |
| *Enterovirus* | 1 (3.1) |
| *Metapneumovirus* | 1 (3.1) |
| *Rhinovirus* ` | 1 (3.1) |
| *Respiratory Syncytial Virus* | 2 (6.2) |
| *Influenza B* | 1 (3.1) |
| *H. Parainfluenza* | 1 (3.1) |
| *Negative* | 21(65.6) |
| *No test done* | 26 (44.8) |
| **Bronchoscopy n= 34** | |
| Normal anatomy | 30 (88) |
| Abnormal branching of the RUL bronchus | 1 (3) |
| Extensive papillomatous disease of trachea, bronchi | 1 (3) |
| Granulation tissue in left main bronchus, | 1 (3) |
| Tracheobronchomalacia right side | 1 (3) |
| **Lung Biopsy n=3** | |
| Chronic lung inflammation | 1 (1.7) |
| CPAM type 1 | 1 (1.7) |
| Lymphocytic Interstitial Pneumonia | 1 (1.7) |

**Table 5**
**Spirometry Results - Comparing first ever and Last 2019 Results, n=33**

| | **Mean (SD) Z score** | **P value** |
|---|---|---|
| **FEV1, 1** | -4.3 (1.0) | 0.0003 |
| **FEV1, 2** | -3.9 (1.0) | |
| **FVC1, 1** | -3.8 (1.4) | 0.0002 |
| **FVC1, 2** | -3.1 (1.0) | |
| **FEV1/FVC, 1** | -1.83 (1.9) | 0.19 |
| FEV1/FVC, 2 | -2.0 (1.8) | |

*The table shows comparison of first ever and last spirometry of 2019 results. FEV1, 1 – Forced expiratory volume in the first second of the first ever spirometry test done. FEV1, 2 - Forced expiratory volume in the first second of the last spirometry in 2019. FVC1,1 – Forced vital capacity of first ever spirometry test done for patient. FVC1,2 – Forced vital capacity of last spirometry test in 2019. FEV1/FVC, 1 – First ever test done. FEV1/FVC, 2 – last test done in 2019*

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## Appendices

## Appendix A

Data Collection Sheet

Data collection Sheet Number : _____

Date of Collecting Data: _____

Date of last clinic attendance: _____

Total attendances in a year: _____

Name and designation of person collecting data _____

**Inclusion criteria:**

1. Any child diagnosed with Bronchiectasis meeting the study definition:

| | |
|---|---|
| Bronchiectasis | Recurrent (>3 episodes/year) wet or chronic (>4-8 weeks) productive/wet cough; with or without: exertional dyspnea, airway hyper-responsiveness, recurrent chest infections, growth failure, clubbing or chest deformity<br>AND<br>Consistent radiological features on chest HRCT scan |

**Exclusion Criteria**

Any child with diagnosis of cystic fibrosis as follows should not be enrolled:

1.1 Positive sweet test: Cl >60 mmols/l
1.2 Fecal Elastase < 200 micrograms/ml

**Patient details**

1. Unique identifier (with link log to hospital number):
2. Date of birth:
3. Age:
4. Sex:
5. Weight:
6. Height:
7. BMI:
8. WFH z score:
9. Age at diagnosis:
10. Residence:
11. HIV status:

**Aetiology**

1) Post infectious Bronchiectasis
    i) Viral : RhinoVirus, AdenoVirus, Other:
    ii) HIV Yes NO Exposed
    iii) Bacterial: Tuberculosis, Staph, Other:
    iv) Diagnosis: NPA, Sputum MCS, BAL, lung biopsy
2) Foreign body inhalation: YES NO Bronchoscopy confirmed Yes NO
3) Primary immunodeficiency: YES NO Immune work up YES NO
4) Primary Ciliary dyskinesia: Yes / NO Nasal mucosa brushings Yes NO
5) Gastro-Oesophageal Reflux Disease : YES NO
    i) Milk scan – Reflux: YES NO
    ii) MBS Aspiration: YES NO
6) Anatomical abnormality: YES If Yes specify NO
7) Other:
8) Cause unknown:

**Clinical Symptoms**

1) Cough YES NO
    i) Dry / Wet / Both
    ii) Sputum - Daily / Weekly / Seldom / only when sick
    iii) Character - Yellow / Whitish / greenish / Blood stained / Mucoid
    iv) Amount - Teaspoon / Half sputum jar / Full sputum jar
2) Wheeze YES NO
    i) Frequency - Daily Once / Daily multiple / Weekly / Seldom / Only when sick
    ii) When is wheeze worse: Morning / during the day / Evening / After Exercise
3) Exercise intolerance:
    i) 6MWT Yes NO

ii) Distance walked comfortably:

4) Maintenance treatment YES NO
   i) Treatment given Antibiotics / Azithromycin / SABA / ICS / Other
5) Exacerbations
   i) Number in 12 months: None / one / Two / More than 2
   ii) Treatment Yes NO
   iii) Treatment Given Antibiotics / SABA / ICS
6) Recurrent / Persistent sinusitis YES / NO
7) Recurrent / Persistent Otitis Media YES / NO

**Clinical signs**

**i)** Finger Clubbing Yes NO
ii) Chest hyper inflated YES NO
iii) Crepitations YES NO
iv) Wheezing YES NO
v) Cor Pulmonale YES NO
vi) Neuro developmental delay YES NO

**Use of Home oxygen Yes NO**

i) Saturation in Room Air < 92% > 92 %
ii) Duration of use <1 year >1 year
iii) Period of Use: 24/7 During sleep After exercise

**Past Medical History**

**1)** Early Life History:
   i) Prematurity: Y / N
   ii) Gestational age at birth < 28 weeks 28-34weeks > 34-37weeks >37weeks
   iii) Perinatal complications: YES NO If yes, specify
      (a) Ventilated Y / N If yes, number of days:
      (b) Mode of Oxygen therapy: NPO2 CPAP IPPV HFOV
      (c) Breast feeding YES NO
         (i) Duration:
            1. 6 months
            2. 6-12 months
            3. > 12 months
      (d) Maternal smoking during pregnancy YES NO
**2) HIV status:**
   i) Negative
   ii) Infected

iii) Exposed Uninfected
iv) Unknown

**3) Age at diagnosis: Specify**

**4) Previous admissions to hospital: YES NO**

i) Respiratory illness ever: YES NO
ii) Number needing admission ever:
iii) Treatment given: Antibiotics ICS SABA
iv) Organism isolated:
v) Specimen: NPA Sputum Tracheal Aspirate

5) **Extra pulmonary Illnesses:** YES NO

**6) Family History:**

7) **Chronic lung Disease:** Yes NO If Yes specify

**8) Environmental Exposures:**

i) Home tobacco exposure: YES NO
ii) Cooking Fuel: Electricity, paraffin, wood, Gas, Other
iii) Pesticides: YES NO
iv) Industrial fumes: YES NO
v) Pet at home: Dog, cat, bird, Rabbit, Other
vi) Other exposures:

**Radiology Findings:**

**1) Chest Xray findings**

i) Focal Disease
ii) Diffuse Disease None

2) **CTSCAN chest findings**: Specify
3) **Milk scan** : Reflux / Reflux and Aspiration
4) **Modified Barium Swallow**: Aspiration / Silent aspiration / No aspiration

**5) Lung Function tests at baseline and last in 2019:**

i) $FEV_1$ 1 / $FEV_1$ 2: SD
ii) FVC 1 / FVC 2: SD
iii) Ratio 1 / ratio 2: SD
iv) BDR 1 / BDR 2: SD
v) Interval between results (months)

**6) Histology:**

i) Lung Biopsy YES NO
ii) Results:

**7) Laboratory results:**

i) Last sputum 2019 Done Not done
ii) Organism isolated _____

**8) Bronchoscopy:**

i) Airway Abnormality YES NO
ii) Fistula excluded YES NO
iii) Foreign body excluded YES NO

**9) BAL results:**

i) Organism isolated
ii) Gen Expert result Positive Negative
iii) Fungal Positive YES NO
iv) Virus Positive YES NO
v) PCP Positive YES NO
vi) EBV Positive YES NO
vii) CMV Positive YES NO
viii) NTM Positive YES NO

**Appendix B**

**Author guidelines for selected journal for publication**

**Manuscript preparation** top

Presentation of manuscripts should be consistent with the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, as recommended by the International Committee of Medical Journal Editors (ICMJE).

Brief requirements for journal articles are summarised in the following table. The requirements are outlined in more detail below.

| Article type | Word limit | Figures and tables* | References | Online supplement | Abstract |
|---|---|---|---|---|---|
| Original research | 3000 | 8 | 40 | Accepted | Yes, 250 words |
| Editorials | 1500 | 2 | 30 | Not accepted | No |
| Review and series articles | 5000 | 5 | 200 | Accepted | Yes, 250 words |
| Research letters | 1200 | 1 | 15 | Not accepted | No |
| Correspondence | 800 | 1 | 10 | Not accepted | No |
| Task force reports, guidelines and consensus statements | 8000 | 15 | 250 | Accepted | Yes, 250 words |

*The number of figures and tables in the above summary refers to the combined number; for example, letters can have either one figure or one table, not one of each.

For further general guidance on how to write papers, please refer to: Sterk PJ, Rabe KF. The joy of writing a paper. Breathe 2008; 4: 224-232, and guidelines for authors on how to write scientific articles to be published in English at www.ease.org.uk/publications/author-guidelines

Authors are reminded that they should not imply that any opinions or views expressed in their article are those of the journal.

***General***

- Write the manuscript in UK English.
- The manuscript file you submit must be saved in rich text format (.rtf) or as a Microsoft Word document (.doc or .docx).
- Describe abbreviations and unusual terms at the first time of use.
- Symbols as defined by the ad hoc working group of the Commission of the European Communities (see Eur Respir J 1993; 6: Suppl. 16) are recommended.
- Système International (SI) units are recommended.
- Equations should be created as normal text.

***Title page***

- Provide a concise and informative title, limited to 90 characters (including spaces).
- Include a list of all contributing authors names in full and all of their affiliations, with a clear indication of who is associated with each institution.
- Supply the full correspondence details for one corresponding author, including e-mail address. The corresponding author indicated in the manuscript does not necessarily need to be the submitting author. Shared first and/or last authorship, indicated by a footnote to the author list, is permitted for academic credentials. The journal strictly allows only one corresponding author, with exceptions limited only to ERS documents/guidelines jointly developed with other societies, for which shared corresponding authorship has been agreed upon with the publications office and editors prior to submission.
- Provide a 256-character (including spaces) summary of the "take home" message of your paper, which can be used to publicise your study *via* social media.

***Tables***

- Insert tables into the main text document, before the references, using the Table function in your word processing package. Do not supply tables in a separate file.
- Number tables consecutively with Arabic numerals.
- Limit data to a sensible number of significant figures.
- Avoid large tables if possible. Large tables are difficult to display on small screens or A4 printouts.
- Provide a clear footnote for each table, making sure all abbreviations and symbols used are defined.

- For reference numbering schemes, citations made in tables should continue in numerical order from the point in the main body text where the table is first cited.

***Figures***

***FILE FORMAT AND METADATA***

- Figures must be uploaded as separate files, not as part of the main manuscript text document. During the upload process, you should fill in the "Caption/legend" box including the figure number and legend, so that reviewers know which figure they are looking at. Alternatively, you may add the figure captions at the end of the main manuscript text.
- Figures should be limited to a maximum of four panels.
- Supply line-art figures in EPS, Adobe Illustrator (.ai) TIFF, JPEG or PNG format. Please ensure image files are not layered and that the image size does not exceed 180 x 230mm. Graphs or bar charts may be supplied in Excel or similar spreadsheet format.
- Supply halftone and photographic images in TIFF, PNG, JPEG or EPS format. Minimum resolution should be 300 dpi at the final typeset size (90 mm to 180 mm wide).
- As an alternative to the above, you can supply figures as a single- or multi-page PDF. However, you must include figure legends within the PDF, as our submission software will not add them.
- If your halftone or photographic image features text or arrows marking out particular features, you may wish to supply an additional copy as a layered Adobe Photoshop (.psd) file, labelled as "Supporting document (not for publication)". This helps our production staff to ensure optimal reproduction of your figure.
- If your figures were originally created in another format that contains extra information (e.g. embedded data in an Excel graph), consider supplying them as supplementary material (Original Research Articles and Review articles only).

***SIZE AND QUANTITY***

- Figures constitute a key element of manuscripts submitted to the ERS research journals. However, figures should be limited (both in size and number) to those required to show the essential features described in the manuscript.
- Avoid large figures comprising many individual parts: as a maximum, each individual figure must fit to a single PDF page of the journal, with sufficient space for its accompanying caption.

- If you have a large number of figures, consider publishing some of them as an online supplement.

***FIGURE PRESENTATION***

- All submitted figures must be clearly named and numbered.
- Whether for images, drawings or graphs, use no more than four panels for a single figure. These should be labelled as a), b), c) and d).
- In photographic and halftone images, show only the areas of interest with enough surrounding area for orientation purposes.
- Radiographic images should be of high quality and combined into one array, such as posteroanterior and lateral views. Each panel should be sized identically.
- When several photographic or halftone images of a given type are being shown, please reproduce them all at the same magnification.
- Photomicrographs must have internal linear scale markers (scale bars), since the size and magnification may be altered when the figure is printed or displayed on screen.
- Images should correspond in appearance to the tonal relations of the original radiograph (*i.e.* showing the bones white on a dark background), with the patient's right to the observer's left. CT scans and magnetic resonance images should employ the internationally accepted 'view from below'.
- Label your images such that all important details are clearly marked, but avoid obscuring large areas of the images with excessive labelling.
- Use a sans serif font (such as Arial or Helvetica) for labelling, and ensure that the font is legible, of reasonable size and uniform throughout all the figures in your manuscript.
- Ensure that bar charts and graphs have a white background, with no shading or gridlines.
- Use colour or greyscale shading on bar charts and graphs (different weights can be used, e.g. from 0% (white) to 100% (black) for purposes of differentiation), in preference to hatching and patterning.
- Do not use three-dimensional effects in the presentation of bar charts.
- For reference numbering schemes, citations made in figures should continue in numerical order from the point in the main body text where the figure is cited.

***GUIDELINES FOR HANDLING IMAGE DATA***

- If an image has been enhanced electronically, please explain the alterations that have been made and submit the original image along with the enhanced one. Keep an

electronic set of original images, since our reviewers might ask you to modify their content and the display modus.

- The Council of Science Editors has established four basic guidelines for handling image data, which authors submitting to the ERS research journals are urged to comply with. 1) No specific feature within an image may be enhanced, obscured, removed or introduced. 2) Adjustments of brightness, contrast or colour balance are acceptable if they are applied to the whole image and as long as they do not obscure, eliminate or misrepresent any information present in the original. 3) The grouping of images from different parts of the same gel, or from different gels, fields or exposures must be made explicit by the arrangement of the figure (*e.g.* by using dividing lines) and in the text of the figure legend. 4) If the original data cannot be produced by an author when asked to provide it, the acceptance of the manuscript may be revoked.

***CAPTIONS***

- Provide a clear caption for each figure.
- Captions should be brief and not repetitive of information given in the text.
- All abbreviations should be expanded.
- Where appropriate, captions should include the imaging technique used, the body part imaged and any noteworthy details.
- Mention any use of internal scale bars.

***Acknowledgements***

- Acknowledgements should be grouped into a single paragraph placed after the Discussion section.
- Only acknowledge people who have made substantial contributions to the study, and provide the affiliation of those you name.
- Provide the names and affiliation details of members of collaborating bodies.
- Financial support for the study should be acknowledged in a separate support statement; financial support provided to individuals must be disclosed on the conflict of interest declaration.

**References**

- Number references consecutively in the order in which they first appear in the text, using full-sized Arabic numerals in square brackets to cite references.

- The first three authors should be listed followed by et al.
- References should contain at all the information shown in the following examples:

    1. Bannerjee D, Khair OA, Honeybourne D. Impact of sputum bacteria on airway inflammation and health status in clinical stable COPD. Eur Respir J 2004; 23: 685-692.

    2. Bourbon J, Henrion-Caude A, Gaultier C. Molecular basis of lung development. In: Gibson GJ, Geddes DM, Costable U, Sterk PJ, Corrin B, eds. Respiratory Medicine. 3rd Edn. Edinburgh/Philadelphia, Elsevier Science, 2002; pp. 64-81.

- Documents published online, and individual web pages, should be listed in the reference list, not in the text, and only used when an original citation is unavailable; citations should contain at all the information shown in this example (include the author of the webpage, its title, the URL on which the cited material can be found, and the dates on which the webpage was last accessed by you, and on which it was last updated):

    3. WHO. Severe Acute Respiratory Syndrome (SARS). www.who.int/csr/sars/en/index.html. Date last updated: June 1 2004. Date last accessed: June 1 2004.

- References to websites as a whole or sections of websites (rather than particular pages or documents on a website) should be included directly in the text:

    ...data was sourced from the WHO Global Health Observatory (www.who.int/gho/en/)...

- Works that have not yet been accepted for publication and personal communications should not appear in the reference list. These should be mentioned directly in the text.
- A copy of any paper cited as "in press" and not yet available online should be uploaded to the submission platform as supporting material.

**Original articles** top
Original articles should not exceed 3000 words (you do not need to include the abstract, references, tables and figure captions in this word count). If your manuscript exceeds this limit, please state the final word count and explicit reasons for exceeding the limit in your covering letter.

The total number of figures and/or tables should be limited to no more than eight. Large figures with more than four parts should be avoided: these can be presented as online supplementary material. More information regarding figures can be found above.

***Abstract***

Please provide an abstract of 250 words or fewer, which is easily understood without reference to the text (see Ann Intern Med 1987; 106: 598-604).

The abstract should have four separate paragraphs, which correspond to: the question addressed by the study; materials/patients and methods; results; and the answer to the question. One or two sentences of background information can be included in the opening paragraph if necessary. The question and answer should be the same as those in the text.

Graphical abstracts can be accepted and will be published as supplementary material. Graphical abstracts must be submitted for peer review and cannot be provided after acceptance.

Include only the most important numbers and results, and avoid using abbreviations.

***Introduction***

In the introduction, state the question you asked (or hypothesis to be tested) and your considerations leading to the formulation of the question. Give only pertinent references.

***Material and methods***

***STUDY SUBJECTS OR ANIMALS***

- Clearly describe how the subjects or experimental animals were identified, including the control subjects when used. For animals, see Laboratory Animals 1985; 19: 106-108.
- Clearly state the eligibility criteria for cases and controls in observational studies, or for subjects in clinical trials.
- When reporting studies on human subjects, authors should indicate whether the study procedures were approved, or were exempt from review, by the responsible national or institutional review committee. If no formal ethics committee was available, a statement indicating that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki should be included. Written informed consent must also have been obtained from all subjects and this must be clearly indicated in the paper. See also guidance on the reporting of clinical trials, below.
- Animal experimentation must have been performed according to the Declaration of Helsinki conventions for the use and care of animals.
- Provide details of the species and/or strain and number of animals involved in the study.
- The editors will reject work that does not conform to acceptable ethical criteria.

***STUDY DESIGN***

- Clearly state the main study objective(s).
- Consider sample size and whether you have enough subjects to reliably address the research question.

- Manuscripts reporting clinical trials should include details of the sample size calculation (*i.e.* the expected effect size, power, level of statistical significance and one- or two-sided test).
- For systematic reviews, make sure that the keywords used to search electronic medical databases cover different terminology (for example, tumour or cancer) and spelling (for example, randomised or randomized).

***METHODS***

- Provide an overview of the main tests or experiments.
- Describe the methods and apparatus in sufficient detail to allow other workers to evaluate or reproduce the tests/experiments.
- For methods that have been published before, provide a reference only, or a reference and brief description.
- Identify drugs and chemicals, including generic name, dosage and route of administration.
- Provide manufacturers' names and addresses (city and country) for equipment, drugs, chemicals and software as necessary, but not in a separate section.

***ANALYSIS***

- Clearly state and define the main outcome measure(s).
- Briefly state the statistical methods used during the analysis if they are standard. Describe any new methods and justify their use.
- In the case of single- or multicentre trials with blinded intervention, the code must have been broken at the end of the study in the presence of the responsible investigator of each centre. The code and the data will then be available to each participating centre. The first author should make provisions so that if needed, the data are available to the editors for independent statistical analysis.
- Seek advice from a statistician on the appropriate methods of analysis and whether results have been interpreted correctly.

***Results***

- Keep the results section brief.
- Describe the baseline characteristics or condition of patients or animals.
- Focus on the important results, *i.e.* those that help to address the research question.

- Present most data in figures or tables, not in the text. Use the text to emphasise or summarise the most important observations.

***Discussion***

- At the beginning of the discussion, summarise the main results, and show how they have addressed the research question.
- Make sure that the conclusions are consistent with the results and are pertinent to the research question.
- Describe the limitations of the study and/or analysis, and discuss their possible implications for the conclusions.
- Emphasise the new and important aspects of the study.
- Try to explain contradictory or unexpected results, or discrepancies with previous findings.

**Review and series articles** top

Review articles provide an overview and discussion of recent and current studies/practices in a particular area of respiratory research.

They should include an abstract of no more than 250 words, which provides an overview of the full article and which is easily understood without reference to the text.

Review articles should not exceed 5000 words (you do not need to include abstract, references, tables and figure captions in this word count); if manuscripts exceed this limit, please state the final word count and give your reasons for exceeding the limit in your covering letter.

The total number of figures and/or tables should be limited to no more than five.

Given the nature of review articles, it is appropriate to include a higher number of references than in original articles, but this should not exceed 200 in total.

**Letters and correspondence** top

Research letters are case study articles, preliminary studies or short reports presented in the format of a letter to the editor.

Research letters do not contain an abstract.

Research letters should not exceed 1200 words (you do not need to include references, tables and figure captions in this word count) and should have no more than 15 references. One figure or one table may be included. Figures must be limited to 4 panels (A-D), however a single panel figure is preferred for letters: The Lost Art of Composing Single-Panel Figures

Correspondence can be submitted for discussion of recently published articles and other topical matters; correspondence articles should not exceed 800 words (you do not need to include

references, tables and figure captions in this word count) and should have no more than 10 references. One figure or one table may be included.

The ERS research journals will not publish online supplementary material for letters or correspondence.

**Online supplementary material and video summaries** top
Authors of original or review articles have the option of providing more detailed methodology, supplementary data or figures, and accompanying videos, as an online supplement. This is optional, at the discretion of the author and/or editor. The ERS research journals will not accept supplementary material for editorials, letters or correspondence. Documents should be uploaded as "Supplementary material" during the submission process.

Videos should be a short summary, in English, of the study – they must not go beyond the scope of the paper. These should be submitted alongside the manuscript for peer review, though this may be done at revision stage. If necessary in the submission, a link to an externally hosted video can be included if the file is not able to be uploaded. The video should be no longer than 5 minutes, and should not contain any branding or promotional content, but can include a funding support statement.

Online supplementary material will not be edited by the publications office, and will be published online as it is supplied.

**Guidelines for reporting research findings** top
Randomised controlled trials must conform to the CONSORT statement, which provides a set of recommendations comprising a list of items to report and a patient flow diagram. A completed CONSORT checklist should be included with the submission. A data sharing statement should be included with all clinical trial submissions indicating whether the authors wish to make primary data available to other research groups.
Systematic reviews and meta-analyses should be registered on the PROSPERO database. Reporting should follow PRISMA guidelines. Meta-analysis of observational data should follow MOOSE guidelines. A completed PRISMA or MOOSE checklist should be included with the submission.

For other study designs, authors should consult the following reporting guidelines: studies of diagnostic accuracy (STARD); observational studies in epidemiology (STROBE); standard protocol items: recommendations for interventional trials (SPIRIT) and animal research reporting of *in vivo* experiments (ARRIVE). As above, completed checklists should be included with submissions.
In some cases, the chief editor may require that authors make available the data on which their findings are based, or provide other documentation relating to the protocol of their study.

**Data availability and publication** top
We encourage authors to make the datasets underlying their manuscript available, when this is practical, either publicly or upon request. Datasets can be shared publicly via subject-specific or general online repositories, or by submitting them as online supplementary material. The PLoS journals provide useful guidance on data repositories and sharing.

The ERS research journals encourage data sharing through the Dryad data repository. Dryad is an international repository for the datasets underlying articles in the sciences and medical research. Datasets published by Dryad are accessible to all readers, and the sharing of raw data in this way enables other researchers to validate study findings and perform new analyses.

If you wish to deposit your dataset with Dryad, we can help by creating a "stub" or holding page, ready for you to access and to deposit your data, at the point that your manuscript is accepted for publication in the journal. Although an author fee is payable when depositing data with Dryad, the ERS has allocated funds to cover deposit fees for an introductory period, which will be available on a strictly first come, first served basis.

Authors should still continue to submit supplementary methods, results, figures and tables in the same way for publication as an online article supplement on the journal site; the Dryad repository should be used to archive the datasets that underlie the study published by the journal.

Once you have successfully deposited a dataset, it will be allocated a unique DOI by Dryad, thereby establishing a permanent link that you can use to cite your dataset.

For a more detailed overview of how to deposit your data with Dryad, please click here.

**Registering clinical trials** top

In order to be published in the ERS research journals, any clinical trials started after January 1, 2006 must be properly registered. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioural treatments, process-of-care changes and the like.

The ICMJE accepts registration in any registry that is a primary register of the WHO International Clinical Trials Registry Platform (ICTRP) or in ClinicalTrials.gov, which is a data provider to the WHO ICTRP.

The ICMJE is expanding the definition of the types of trials that must be registered and will begin to implement the World Health Organization definition of clinical trials for all trials that began enrolment on or after July 1, 2008. The World Health Organization's definition of clinical trials is: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes".

The ICMJE does not consider results posted in the same clinical trials registry in which the primary registration resides to be previous publication if the results are presented in the form of a brief (500 word) structured abstract or table (including data on patients enrolled, key outcomes and adverse events). When submitting to the ERS research journals, authors should specify where the clinical trial is registered and disclose all posting in registries of results of the same or closely related work.

For further details on current ICMJE policy, please refer to the ICMJE or N Engl J Med 2007; 356: 2734-2736.

**Authors are reminded that in addition to the above there may be legal requirements regarding registration of clinical trials, and publication of summaries and other material in**

**public repositories. The ERS will not regard any publication of material under these requirements as prior publication.**

**Permission to re-publish materials** top

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**Authorship** top

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Authorship credit should be based on fulfilment of all of the following four criteria:

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2. drafting the article or revising it critically for important intellectual content; and
3. final approval of the version to be published; and
4. agreement to be accountable for all aspects of the work, in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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As manuscripts must have been approved by all authors prior to submission, any changes to the list of authors that are proposed after manuscript submission require written approval from all named authors; this is in accord with the procedures outlined by the Committee on Publications Ethics (COPE).

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Examples of those who might be acknowledged include: people or collaborating bodies who contributed materially to the paper but whose contributions do not justify authorship; a person who provided purely technical help or writing assistance; a department leader who provided only general support.

If the study was performed in collaboration with or on behalf of a particular body (for example, ISAAC), the names and affiliation details of members of that body or group should be listed in an acknowledgements section.

**ORCID** top
The ERS manuscript submission and publishing systems support the use of ORCID researcher identifiers. Authors who wish to have their ORCID associated with their manuscript should log in to the submission system and edit their personal account to include their ORCID and to authorise ORCID to link to their ScholarOne account. This must be done prior to manuscript acceptance.

The ORCID website (orcid.org) contains resources for authors. ERS has also created a brief guide to creating and maintaining your ORCID profile.

**Conflict of interest** top
Any conflict of interest for a given manuscript and for all authors of a manuscript must be dealt with according to the statement of the ICMJE (the 'Vancouver Group') as published in Lancet 1993; 341: 742. Editors and reviewers must disclose to the Chief Editor any personal or financial relationship that could bias their opinion and decision in the peer-review process.
**In the interests of transparency, all authors must provide a written statement as part of the submitted manuscript that details any conflicts of interest they may have.**

Authors must acknowledge all financial support for the work (including, but not limited to, support from pharmaceutical companies and medical device companies) and other financial or personal conflicts of interest that are both connected and unconnected with the work. The author should consider: grants; honoraria; royalties; relevant current/past employment and other affiliations; patents (either pending, issued or licensed); expenses/travel costs paid for conference attendance; drugs/equipment supplied by a particular company; administrative support; and fees for consulting, lecturing, working on speakers' bureaus or advisory boards, and providing expert testimony. It is each author’s responsibility to provide their own written statement. If the author

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**Appendix: Sources of information for statistical analyses, study design and data presentation** top
The statistical advisors of the *European Respiratory Journal* and *ERJ Open Research* recommend the following series of papers on the use of statistics, in particular those articles on repeatability, reproducibility, regression and correlation analyses and confidence intervals, and comparisons of means and proportions.

1. Bland JM, Altman DG. Correlation, regression and repeated data. BMJ 1994; 308: 896.
2. Bland JM, Altman DG. Regression towards the mean. BMJ 1994; 308: 1499.
3. Altman DG, Bland JM. Diagnostic tests 1: sensitivity and specificity. BMJ 1994; 308: 1552.
4. Altman DG, Bland JM. Diagnostic tests 2: predictive values. BMJ 1994; 309: 102.
5. Altman DG, Bland JM. Diagnostic tests 3: receiver operating characteristic plots. BMJ 1994; 309: 188.

6. Bland JM, Altman DG. One- and two-sided tests of significance. BMJ 1994; 309: 248.
7. Bland JM, Altman DG. Some examples of regression towards the mean. BMJ 1994; 309: 780.
8. Altman DG, Bland JM. Quartiles, quintiles, centiles, and other quantiles. BMJ 1994; 309: 996.
9. Bland JM, Altman DG. Matching. BMJ 1994; 309: 1128.
10. Altman DG, Bland JM. The normal distribution. BMJ 1995; 310: 298.
11. Bland JM, Altman DG. Calculating correlation coefficients with repeated observations: Part 1, correlation within subjects. BMJ 1995; 310: 446.
12. Bland JM, Altman DG. Calculating correlation coefficients with repeated observations: Part 2, correlation between subjects. BMJ 1995; 310: 633.
13. Altman DG, Bland JM. Absence of evidence is not evidence of absence. BMJ 1995; 311: 485.
14. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. BMJ 1995; 310: 170.
15. Altman DG, Bland JM. Presentation of numerical data. BMJ 1996; 312: 572.
16. Bland JM, Altman DG. Logarithms. BMJ 1996; 312: 700.
17. Bland JM, Altman DG. Transforming data. BMJ 1996; 312: 770.
18. Bland JM, Altman DG. Transformations, means and confidence intervals. BMJ 1996; 312: 1079.
19. Bland JM, Altman DG. The use of transformations when comparing two means. BMJ 1996; 312: 1153.
20. Altman DG, Bland JM. Comparing several groups using analysis of variance. BMJ 1996; 312: 1472-1473.
21. Bland JM, Altman DG. Measurement error. BMJ 1996; 313: 744
22. Bland JM, Altman DG. Measurement error and correlation coefficients. BMJ 1996; 313: 41-42.
23. Bland JM, Altman DG. Measurement error proportional to the mean. BMJ 1996; 313: 106.
24. Altman DG, Matthews JNS. Interaction 1: Heterogeneity of effects. BMJ 1996; 313: 486.
25. Matthews JNS, Altman DG. Interaction 2: compare effect sizes not P values. BMJ 1996; 313: 808.
26. Matthews JNS, Altman DG. Interaction 3: How to examine heterogeneity. BMJ 1996; 313: 862.
27. Altman DG, Bland JM. Detecting skewness from summary information. BMJ 1996; 313: 1200.
28. Bland JM, Altman DG. Cronbach's alpha. BMJ 1997; 314: 572.
29. Altman DG, Bland JM. Units of analysis. BMJ 1997; 314: 1874.

30. Bland JM, Kerry SM. Trials randomised in clusters. BMJ 1997; 315: 600.

31. Kerry SM, Bland JM. Analysis of a trial randomised in clusters. BMJ 1998; 316: 54.

32. Bland JM, Kerry SM. Weighted comparison of means. BMJ 1998; 316: 129.

33. Kerry SM, Bland JM. Sample size in cluster randomisation. BMJ 1998; 316: 549.

34. Kerry SM, Bland JM. The intra-cluster correlation coefficient in cluster randomisation. BMJ 1998; 316: 1455.

35. Altman DG, Bland JM. Generalisation and extrapolation. BMJ 1998; 317: 409-410.

36. Altman DG, Bland JM. Time to event (survival) data. BMJ 1998; 317: 468-469.

37. Bland JM, Altman DG. Bayesians and frequentists. BMJ 1998; 317: 1151.

38. Bland JM, Altman DG. Survival probabilities (the Kaplan-Meier method). BMJ 1998; 317: 1572.

39. Altman DG, Bland JM. Treatment allocation in controlled trials: why randomise?BMJ 1999; 318: 1209.

40. Altman DG, Bland JM. Variables and parameters. BMJ 1999; 318: 1667.

41. Altman DG, Bland JM. How to randomise. BMJ 1999; 319: 703±704.

42. Bland JM, Altman DG. The odds ratio. BMJ 2000; 320: 1468.

43. Day SJ, Altman DG. Blinding in clinical trials and other studies. BMJ 2000; 321: 504.

44. Altman DG, Schulz KF. Concealing treatment allocation in randomised trials. BMJ 2001; 323: 446-447.

45. Vickers AJ, Altman DG. Analysing controlled trials with baseline and follow up measurements. BMJ 2001; 323: 1123-1124.

46. Bland JM, Altman DG. Validating scales and indexes. BMJ 2002; 324: 606-607.

47. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ 2003; 326: 219.

48. Bland JM, Altman DG. The logrank test. BMJ 2004; 328: 1073.

49. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. BMJ 2004; 329: 168-169.

50. Altman DG, Bland JM. Treatment allocation by minimisation. BMJ 2005; 330: 843.

51. Altman DG, Bland JM. Standard deviations and standard errors. BMJ 2005; 331: 903.

52. Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ 2006; 332: 1080.

53. Altman DG, Bland JM. Missing data. BMJ 2007; 334: 424.

54. Petrie A, Sabin C. Medical Statistics at a Glance. 2nd Edn. Blackwell Publishing, 2006.

55. Kirkwood B, Sterne JAC. Essential Medical Statistics. 2nd Edn. Blackwell Science, 2003.

56. Bland M. Introduction to Medical Statistics. 3rd Edn. Oxford University Press, 2000.

57. Barker DJP, Rose G. Epidemiology in Medical Practice. 5th Edn. Elsevier, 1997.

58. Rothman KJ. Epidemiology: an Introduction. Oxford University Press, 2002.

59. Silman AJ, Macfarlane GJ. Epidemiological Studies: a Practical Guide. 2nd Edn. Cambridge University Press, 2002.