



Epidemiology of bronchiectasis

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Number 6 in the Series “World Bronchiectasis Conference 2024”

Edited by James D. Chalmers, Felix C. Ringshausen and Pieter C. Goeminne

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Shareable abstract (@ERSpublications)

Despite increasing incidence and prevalence, bronchiectasis is probably underdiagnosed in several areas of the globe. Differences in assessment methods, aetiologies, comorbidities, microbiology and access to care explain epidemiological heterogeneity. <https://bit.ly/3WGIEfc>

Cite this article as: Nigro M, Laska IF, Traversi L, *et al.* Epidemiology of bronchiectasis. *Eur Respir Rev* 2024; 33: 240091 [DOI: 10.1183/16000617.0091-2024].

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This article has an editorial commentary: <https://doi.org/10.1183/16000617.0124-2024>

Received: 23 April 2024
Accepted: 5 Aug 2024

Abstract

Bronchiectasis is a chronic respiratory disease characterised by permanent enlargement of the airways associated with cough, sputum production and a history of pulmonary exacerbations. In the past few years, incidence and prevalence of bronchiectasis have increased worldwide, possibly due to advances in imaging techniques and disease awareness, leading to increased socioeconomic burden and healthcare costs. Consistently, a mortality increase in bronchiectasis patient cohorts has been demonstrated in certain areas of the globe, with mortality rates of 16–24.8% over 4–5 years of follow-up. However, heterogeneity in epidemiological data is consistent, as reported prevalence in the general population ranges from 52.3 to more than 1000 per 100 000. Methodological flaws in the designs of available studies are likely to underestimate the proportion of people suffering from this condition worldwide and comparisons between different areas of the globe might be unreliable due to different assessment methods or local implementation of the same method in different contexts. Differences in disease severity associated with diverse geographical distribution of aetiologies, comorbidities and microbiology might explain an additional quota of heterogeneity. Finally, limited access to care in certain geographical areas is associated with both underestimation of the disease and increased severity and mortality. The aim of this review is to provide a snapshot of available real-world epidemiological data describing incidence and prevalence of bronchiectasis in the general population. Furthermore, data on mortality, healthcare burden and high-risk populations are provided. Finally, an analysis of the geographical distribution of determinants contributing to differences in bronchiectasis epidemiology is offered.

Introduction

Bronchiectasis is a chronic respiratory disease characterised by permanent bronchial dilatation evidenced at chest computed tomography (CT), associated with a clinical syndrome featuring daily cough, daily sputum production and a history of pulmonary exacerbations [1]. In the last few decades, bronchiectasis has rapidly moved from being a rare or orphan disease to a global problem, with a large-scale trend towards increasing incidence and prevalence [2]. Contextually, the scientific community has demonstrated growing interest in this condition, as confirmed by the publication of international guidelines and the foundation of several registries worldwide [3–7] Furthermore, numerous translational and clinical research initiatives have been developed in the last few years, aimed at identifying new therapeutics for people suffering from bronchiectasis [8].

Available data on bronchiectasis prevalence are quite heterogeneous, with reported prevalence roughly ranging from 50 to 1000 cases per 100 000 individuals. However, these data are likely to underestimate



bronchiectasis epidemiology for several reasons. First, the definition of bronchiectasis as a clinically and radiologically significant disease requires a chest CT scan to be performed and we can speculate that a proportion of affected patients might not undergo such a radiological test for a variety of reasons [9]. On the other hand, some patients might have radiological evidence of bronchiectasis but no associated signs and symptoms. Secondly, administrative databases may not capture the totality of patients due to an imprecision of assessment methods in the general population, as a recent study identified the poor sensitivity of the International Classification Disease codes ICD-9/10 [10]. Thirdly, patients usually suffer a relevant diagnostic delay, receiving wrong disease labels, such as COPD and/or asthma, and inappropriate treatments for years [9]. Finally, the epidemiology of bronchiectasis can be influenced by external factors with different geographical distributions, such as disease aetiology, comorbidities, microbiology and access to care. All these challenges should be considered when interpreting the results of epidemiological papers on bronchiectasis.

The aim of this narrative review is to provide an overview on bronchiectasis epidemiology through real-world data describing prevalence, incidence, mortality, healthcare burden and high-risk populations associated with this condition.

Search strategy

We conducted a narrative, PubMed-based review of articles mentioning the keyword “bronchiectasis” in combination with the following items: “epidemiology”, “incidence”, “prevalence”, “mortality”, “healthcare burden”, “comorbidities”, “aetiologies”, “microbiology” and “access to care”. Articles focusing exclusively on patients with cystic fibrosis or without radiological confirmation of bronchiectasis were excluded. With the exception of studies on high-risk populations, which occasionally included paediatric patient data, only studies conducted on adults were considered.

Prevalence and incidence

Any examination of bronchiectasis epidemiology should be preceded by the recognition of a number of challenges. Firstly, prevalence data in the general population is only available for a small number of countries, accounting for less than a quarter of the global population, with no information from entire regions of the globe, such as Africa, South America or the Middle East, as displayed in figure 1. Secondly, studies conducted within the same country or in countries expected to be similar, such as Spain and Italy, show consistent differences in prevalence and incidence, as shown in table 1. This effect is probably linked to different database sources and assessment methods. Insurance-based databases are likely to introduce a selection bias in the study population, as included people might undergo medical examinations more frequently and have fewer risk factors than people without stipulated medical insurance. Therefore, this approach may detect patients with radiological evidence of bronchiectasis in the absence of daily signs, symptoms or exacerbations, indicating the likelihood of nonclinically relevant bronchiectasis. Thirdly, some studies conducted using the same database materials, such as the general practitioner (GP)-based studies by QUINT *et al.* [11] in the UK and ALIBERTI *et al.* [12] in Italy, show discrepant results. This could reflect differences in standard operating procedures in primary care settings, hinting at difficulties in the homogenisation of data obtained through these sources. Fourthly, small sample size studies, such as the one conducted by ZHOU *et al.* [13], may lack precision and have limited generalisability. Fifthly, real differences in study populations at a global level in terms of genetics, environmental factors, aetiologies, comorbidities, microbiology and access to care might explain the remaining part of epidemiological diversity.

Considering these caveats, existing data seem to demonstrate that the prevalence of bronchiectasis might be lower in continental Europe (53–362 per 100 000 individuals) [12, 14–16] compared to Asia (76–1249 per 100 000) [17–21]. Interestingly, the UK shows higher prevalence (350–566 per 100 000 women and 281–486 per 100 000 men), with a reported annual increase of 8–20% [11, 22]. In the US, the prevalence increased from 52.3 to 714.0 per 100 000 people between 1999 and 2001 and 2014 [23–25]. An 8-year study detected an overall prevalence of 1106 per 100 000 people between 2000 and 2007 [26]. The global prevalence has consistently increased over time [11, 21, 24]. This effect may be at least in part due to increasing disease awareness and advances in imaging techniques. Overall, bronchiectasis prevalence is higher in women, with reported proportion ranging between 51.6 and 68.0%. Furthermore, prevalence generally increases with age, moving from 4.2–43.4 per 100 000 people aged 18–34 years to 153–1365 per 100 000 individuals older than 65–75 years [11, 15, 18, 23]. Interestingly, some studies have highlighted a higher prevalence in men compared to women in the eldest age brackets [12, 14–16]. The mean age of bronchiectasis patients has increased over time moving from 61 to 68 years in the US and from 64.2 to 67.6 years in Germany [14, 23, 25]. Bronchiectasis seems to be more common in individuals with higher socioeconomic status [11]; however, when an association with COPD exists, it is more likely to occur in people with a lower socioeconomic status [24]. A single study highlighted a significantly higher

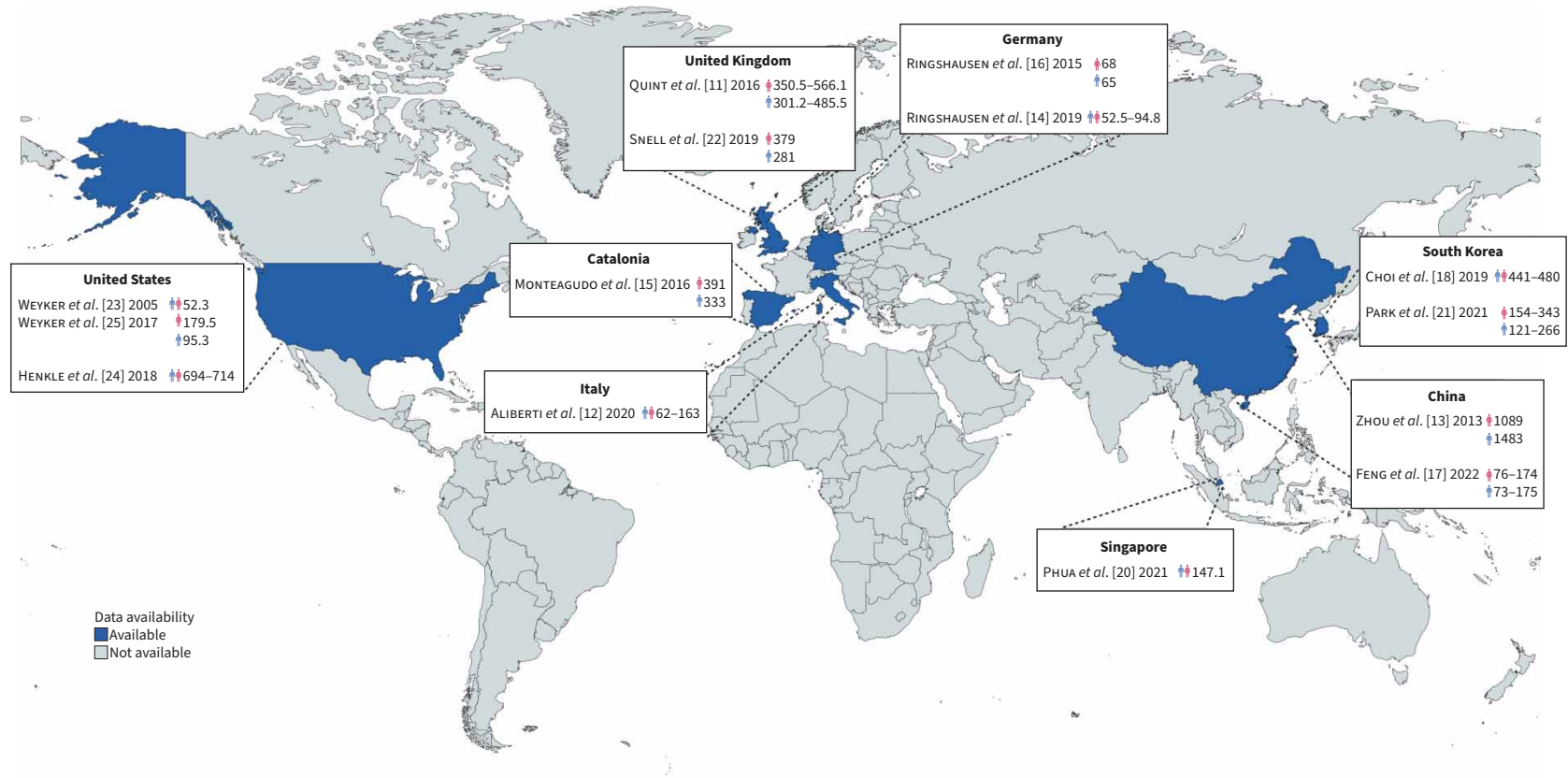


FIGURE 1 Prevalence of bronchiectasis in the general population according to available data. Countries have been coloured in blue if they had at least one available study describing prevalence in the general population. For these countries, available studies are mentioned in the boxes. Numbers are expressed as number of people affected by the disease per 100 000 individuals. The blue and pink indicator represent males and females, respectively; when they are separated, they indicate gender-related prevalences, when together they indicate overall prevalence. Studies including evaluations at more than one timepoint have the minimum and maximum prevalence indicated. Reference numbers follow the same order as the text.

TABLE 1 Incidence and prevalence of bronchiectasis

Country	Study, year	Source	Sample size (n)	Age group	Year	Prevalence (per 100 000)	Incidence (per 100 000 person-years)
Europe							
UK	QUINT [11] 2016	Primary care database (Clinical Practice Research Datalink database)	5.4 million	All	2004	Female: 350.5 Male: 301.2	Female: 21.2 Male: 18.2
					2013	Female: 566.1 Male: 485.5	Female: 35.2 Male: 26.9
	SNELL [22] 2019	Primary care database (The Health Improvement Network records)	5% of UK population (total ~52 million)	All	2004		Overall: 20
					2012	Female: 379 Male: 281	Overall: 33
Catalonia	MONTEAGUDO [15] 2016	Primary care database (Information System for the Development of Research in Primary Care)	5.8 million (80% of the total population)	All	2012	Overall: 362 Female: 391 Male: 333	Overall: 48.1 Female: 49.3 Male: 46.9
Germany	RINGSHAUSEN [16] 2015	Federal Insurance Authority	3 895 272	All	2013	Overall: 67 Female: 68 Male: 65	
	DIEL [52] 2019	Health Risk Institute research database from more than 80 German statutory health insurance companies	3 988 648	All	2011		Overall: 16.77
					2012		Overall: 16.05
2013						Overall: 21.23	
RINGSHAUSEN [14] 2019	Externally validated InGef research database claims data from public health scheme	4 million	All	2009	Overall: 52.5	Overall: 20.88	
Italy	ALIBERTI [12] 2020	Primary care database	1 054 376	≥15 years	2005	Overall: 62	
					2015	Overall: 163 Female: 178 Male: 147	Overall: 16.3 Female: 18.2 Male: 14.1
Poland	NIEWIADomsKA [31] 2016	National Health Found and Mz/Szp-11 reports	4 635 882	≥19 years	2006		Overall: 19.9 Female: 21.4 Male: 18.7
					2007		Overall: 25.1 Female: 27.3 Male: 23.4
					2008		Overall: 22.2 Female: 23.0 Male: 22.3
					2009		Overall: 23.7 Female: 26.0 Male: 21.7
					2010		Overall: 21.1 Female: 22.2 Male: 20.6
America							
USA	WEYCKER [23] 2005	Healthcare claims	5.6 million	≥18 years	1999–2001	Overall: 52.3	
	SEITZ [26] 2012	5% sample of the Medicare outpatient claims database	>2 million	≥65 years	2000–2007 (total 8-year period)	Overall: 1106 Female: 414.8 Male: 245.7	
					2000	Female: 322 Male: 223	
					2007	Female: 553 Male: 388	
WEYCKER [25] 2017	Truven Health Analytics MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases	Prevalence: 33.2 million Incidence: 23.7 million	≥18 years	2013	Overall: 138.6 Female: 179.5 Male: 95.3	Overall: 28.5 Female: 33.6 Male: 23.0	
HENKLE [24] 2018	40% of Medicare enrollees with prescription drug plans	NA	NA	≥65 years	2006–2014	Overall: 701 Female: 802 Male: 617	
					2012	Overall: 694	
					2013	Overall: 694	
					2014	Overall: 714	

Continued

TABLE 1 Continued

Country	Study, year	Source	Sample size (n)	Age group	Year	Prevalence (per 100 000)	Incidence (per 100 000 person-years)
Asia							
China	ZHOU [13] 2013	Urban population–based cross sectional survey of bronchiectasis	10 811	≥40 years	2002–2004	Overall: 1248.7 (135/10 811) Female: 1088.8 (70/6429) Male: 1483.3 (65/4382)	
	FENG [17] 2022	Urban Employee Basic Medical Insurance and Urban Resident Basic Medical Insurance in China	>380 million	≥18 years	2013	Overall: 75.48 Female: 76.12 Male: 73.42	
					2014	Overall: 112.61 Female: 115.45 Male: 109.71	
					2015	Overall: 120.41 Female: 119.19 Male: 122.03	
					2016	Overall: 131.97 Female: 133.13 Male: 131.20	
					2017	Overall: 174.45 Female: 173.60 Male: 175.03	
Singapore	PHUA [20] 2021	Ministry of Health-hosted administrative database	NA	All	2007		Overall: 13.9
					2008		Overall: 12.5
					2009		Overall: 12.4
					2010		Overall: 11.4
					2011		Overall: 12.4
					2012		Overall: 11.0
					2013		Overall: 9.6
					2014		Overall: 9.4
					2015		Overall: 9.5
					2016		Overall: 10.6
South Korea	CHOI [18] 2019	Health Insurance Review and Assessment Service, National Patient Sample	1.4 million	≥20 years	2012–2017	Overall: 147.1	Overall: 10.6
					2012	Overall: 464	
					2013	Overall: 464	
					2014	Overall: 441	
					2015	Overall: 455	
					2016	Overall: 474	
					2017	Overall: 468	
	PARK [21] 2021	National Health Insurance Service–National Sample Cohort data	1 025 340	All	2007	Female: 154.3 Male: 120.9	
					2009		Female: 183 Male: 174.5
					2015	Female: 343.1 Male: 266.4	Female: 150.3 Male: 126.6

Studies are grouped according to the geographical area in which they have been conducted (*i.e.* continents and countries). NA: not available/applicable.

prevalence of bronchiectasis in Asian patients compared to people of other ethnicities [26]. Finally, three studies have measured the prevalence of bronchiectasis in people undergoing CT scans in the context of a lung cancer screening programme [27–29]. Reported prevalence was 9.1% in Korea, 11.7% in Spain and 23% in the US. In these studies, patients with bronchiectasis were generally older and had a more extensive smoking history compared to other people, but no information on the clinical significance of bronchiectasis in these patients was provided [28, 29].

Incidence seems to be distributed with a narrower range of variability across geographic areas, with most regions ranging between 9.4 and 48.1 new cases per 100 000 person-years [11, 12, 15, 20, 22, 25, 30, 31]. In contrast, in 2009, South Korea showed an unexpectedly high incidence of 183 and 175 new cases per

100 000 women and men, respectively [21]. Change of incidence over time was not uniform, but most studies conducted in the UK and Europe found a trend towards growing incidence [11, 22, 30, 31]. This was not the case of some Asian countries, namely Singapore and South Korea, in which incidence seems to have decreased [20, 21]. Similar to prevalence trends, incidence is higher in women at all time-points and increases with age until 79 years [11, 12, 15, 20, 21, 25, 30, 31]. Interestingly, an incidence decline can be noted in people older than 80 years in the UK and Germany and in those older than 85 years in Italy [11, 12, 30].

Mortality

Bronchiectasis patients have a higher mortality rate than the general population [32]. However, studies investigating mortality are heterogeneous in terms of inclusion criteria, assessment methods, associated conditions and follow-up periods, making overall results essentially incomparable. Furthermore, mortality is influenced by the above-mentioned prevalence increase, as a UK population study demonstrated a 3% increase per year in the annual mortality rates between 2001 and 2007 [22, 33].

Published mortality rates are reported in table 2. Different continental European cohorts showed mortality rates ranging from 16% to 24.8%, with follow-up periods of 4.0–5.18 years [34–37]. In the UK, the reported mortality rate in the general population was 1.68 per 100 000 individuals, accounting for 0.18–0.3% of all deaths [22, 33]. In cohorts with longer follow-up periods (4.0–18.8 years), the reported mortality rates were 10.2–29.7% [38–40]. Greater heterogeneity was highlighted in Asia and Australia, with mortality rates ranging between 2.3% and 21% with follow-up periods of 1–10 years [32, 41–47]. In Brazil, a retrospective cohort study reported an anomalously high mortality rate of 38.6% [48]; however, a successive prospective study enrolling 120 bronchiectasis patients demonstrated a probably more reliable 10.8% mortality rate over a 3-year follow-up [49].

Healthcare costs and utilisation

Bronchiectasis represents a relevant burden on healthcare systems [50]. In the US between 1999 and 2001, annual health-related costs of bronchiectasis patients were \$630 million higher than those without the disease [23]. A similar trend was observed in Europe. In Italy (2016–2018), the mean annual expenditure was €3539 for bronchiectasis patients in the first year after diagnosis, 1.9 times higher than asthmatic patients, but 29% lower than those with COPD. Similarly, in Germany (2012–2015), the total direct expenditure per patient was nearly one third higher in bronchiectasis patients compared to matched controls [51, 52].

Hospital admission costs represent a significant contributor to total medical expenditures, ranging from 20% to 55.8–81.2% of reported costs [20, 53]. Notably, hospitalisation-at-home seems to further increase costs [54]. Outpatient costs are mainly linked to drug prescriptions, especially antibiotics, and account for up to 41% of total expenditures [18, 52]. Indirect costs seem to be relevant as well. A German study estimated an average of 40.5 of sick-leave days during a 3-year follow-up period, equating to indirect costs of €4230.49 [52]. These findings were partially confirmed by a Spanish study enrolling hospitalised bronchiectasis patients that reported an average of 13.4±9 sick-leave days for 7.2% of patients and 6.2±4.9 days for their caregivers, accounting for additional expenditures of €776.9±520.6 and €356.5±286.6, respectively [54].

Overall, bronchiectasis-related costs seem to have increased over time. A Chinese study highlighted a 2.18-fold increase of total annual *pro capita* costs and a 1.83-fold increase in inpatient-related costs between 2013 and 2017 [17]. Similarly, in Singapore (2007–2017), the annual inpatient costs rose by 5% annually [20]. In the UK, bronchiectasis-related intensive care unit (ICU) admissions increased by 8% annually between 2009 and 2013, with an estimated increase of annual costs from £189 144 to £298 967 [55]. However, against the trend, in Spain overall costs decreased between 2004 and 2013 [56].

Populations at high risk for developing bronchiectasis

Some populations living in specific areas of the globe have higher risk of developing the disease, with interesting mixed outcomes.

In Australia, Indigenous communities living in the Northern Territory have a higher risk of developing bronchiectasis, representing the 79.3–97.0% of cases in this area [57–59]. A possible association with human T-cell lymphotropic virus seropositivity, far higher in Indigenous people compared to non-Indigenous Australians, was highlighted in some studies [60, 61]. Estimated prevalence in these communities reached 1030–1940 per 100 000 individuals, was higher in women and reached its peak at 50–59 years of age. Furthermore, the age-adjusted prevalence was significantly higher in the urban Darwin

TABLE 2 Mortality of bronchiectasis

Country	Study, year	Study design	Follow-up (years)	Sample size (n)	Study period	Mortality estimate	Measure of effect	Main causes of deaths
Europe								
UK	SNELL [22] 2019	Retrospective (GP data)	1	~52 million (5% of UK population) 54 071 900	2012	0.3%	Deaths in 2012, %	NA
	ROBERTS [33] 2010	Retrospective (Office of National Statistics data for England and Wales)	1		2007	1.68%	Deaths per 100 000	NA
	LOEBINGER [38] 2009	Retrospective	13	91	1994–2007	29.7%	Deaths of cohort, %	Respiratory related (70.4%); renal failure and colon cancer (7.4%); haemoptysis, heart failure, cerebrovascular accident, liver metastasis and pulmonary embolism (3.7%)
	ELLIS [39] 2016	Retrospective	18.8	74	1994–2013	36%	Deaths of cohort, %	Respiratory related (69.2%)
	CHALMERS [40] 2014	Prospective (BSI derivation cohort)	4	608	2008–2012	10.2%	Deaths of cohort, %	Respiratory related (51.5%); myocardial infarction (19.3%); malignancy (12.9%); heart failure, stroke and sepsis (3.2%); pulmonary embolism, trauma, alcoholic liver disease and post-operative complications (1.6%)
Belgium	GOEMINNE [34] 2014	Prospective	5.18	245	2006–2012	20.4%	Deaths of cohort, %	Respiratory related (58%); cardiovascular (16%); unclear (12%); neurological (4%); gastrointestinal, nephrological, haematological, euthanasia and intoxication (2%)
Poland	NOWIŃSKI [35] 2021	Prospective	5	93	2015–2019	16%	Deaths of cohort, %	NA
Spain	MARTÍNEZ-GARCÍA [36] 2014	Retrospective (Seven Spanish hospitals (FACED derivation cohort))	5	397	Before 2005	24.8%	Deaths of cohort, %	Respiratory related (42.9%); malignancy (9.1%); cardiovascular disorders (9.1%)
Turkey	ONEN [37] 2007	Prospective	4	98	2000–2005	16.3%	Deaths of cohort, %	Pulmonary arrest or cardiopulmonary arrest related to bronchiectasis (100%)
Asia Pacific								
Australia	Darwin: urban Darwin: rural East Arnhem Katherine	GIBBS [47] 2024	Retrospective (Hospital medical records)	23 722		7.5%	Mean annual mortality	NA
						4.5%	Mean annual mortality	
						3.2%	Mean annual mortality	
						4.9%	Mean annual mortality	
Australia	REES [46] 2023	Retrospective	4	145	2015–2020	21%	Deaths of cohort, %	NA
China	TANG [41] 2017	Retrospective	5	89	2003–2008	13.5%	Deaths of cohort, %	NA

Continued

TABLE 2 Continued

Country	Study, year	Study design	Follow-up (years)	Sample size (n)	Study period	Mortality estimate	Measure of effect	Main causes of deaths
China	WANG [42] 2021	Prospective	1.3	1234	2013–2019	15.2%	Deaths of cohort, %	NA
India	DHAR [44] 2023	Prospective	At least 1 year (cumulative observation time of 15 479 months)	1018	2015–ongoing	2.3% Ages: 18–40 years 0.5% 41–60 years 3.5% 61–80 years 8.1% >80 years 23.5%	Deaths of cohort, %	NA
Singapore	YOUNG [45] 2021	Prospective	2.4	168	2015–2020	10.7%	Deaths of cohort, %	Pneumonia (22.2%); bronchiectasis (5.6%); colorectal cancer (5.6%); unknown (66.7%)
South Korea	LEE [43] 2021	Retrospective (National Health Insurance Service–Health Screening Cohort)	10	2769	2004–2016	14.8%	Deaths of cohort, %	Chronic lower respiratory disease (13.9%); other malignancies (17.1%); lung cancer (13.0%); cardiovascular disease (10.0%); cerebrovascular disease (5.9%); pneumonia (5.6%); tuberculosis (2.2%); diabetes mellitus (2.2%); hypertension (0.7%); other (28.6%)
South Korea	CHOI [32] 2021	Retrospective (National Health Insurance Service–National Sample Cohort)	10	14 823	2005–2015	15.2% 19.6% Male 11.0% Female 2505 3362 Male 1759 Female	Deaths of cohort, % Deaths in 100 000 patients/year	Malignancy (29.7%); respiratory related (19.8%); cardiovascular diseases (17.8%); injury, poisoning and external causes (overall 7.3%)
South America								
Brazil	MACHADO [48] 2018	Retrospective	5.5±2.3	70	2008–2016	38.6%	Deaths of cohort, %	Acute infectious exacerbation (60.7%)
Brazil	MATEUS [49] 2022	Prospective	3	120	2017–2020	10.8%	Deaths of cohort, %	Circulatory system related (30.8%); infectious and parasitic diseases (23.1%); malignancy (15.4%); digestive system diseases (15.4%); respiratory system diseases (7.7%); external morbidities and mortality (7.7%)
Studies are grouped according to the geographical area in which they have been conducted (<i>i.e.</i> continents and countries). BSI: bronchiectasis severity index; FACED: forced expiratory volume in 1 s, age, chronic colonisation by <i>Pseudomonas aeruginosa</i> , radiological extension and dyspnoea; GP: general practitioner; NA: not available/applicable.								

region compared to rural districts (1800–3600 *versus* 500 per 100 000) [47, 61]. Limited access to healthcare and higher rates of acute respiratory infections, possibly linked to overcrowded accommodation, were the main determinants of the lower life expectancy of Indigenous people compared to non-Indigenous Australians (men 66.6 *versus* 78.1 years, women 69.9 *versus* 82.7 years) [57]. Interestingly, these patients had lower FACED (forced expiratory volume in 1 s (FEV₁), age, chronic colonisation by *Pseudomonas (P.) aeruginosa*, radiological extension and dyspnoea) scores despite having poorer lung function, more exacerbations and poorer prognosis [62, 63]. Mortality rates of Indigenous people with bronchiectasis ranged between 34.2% and 42.5%, with an estimated annual mortality of 4.5–7.5% (see table 2) [47, 60, 61]. The mean age of death was 16–20 years lower in Indigenous compared to non-Indigenous people, and was lower in rural areas compared to the urban Darwin region (60.3 *versus* 67.8 years) [47, 62, 63].

Māori and Pacific Islanders (PIs) represent two distinct high-risk populations, as cohort studies demonstrated that they represent 14.4–27% and 22.9–41% of bronchiectasis patients in New Zealand, despite representing a lower proportion of the local population according to census data (15% and 17%, respectively) [64, 65]. Māori and PI bronchiectasis patients had higher socioeconomic deprivation scores and worse lung function compared to the general population [64, 65]. When compared to Indigenous Australians, Māori and PI people had better lung function and fewer exacerbations, but the overall respiratory-related mortality was similar [62].

In Alaska, the prevalence of bronchiectasis patients was higher in people living in the Yukon Kuskokwim Delta area, despite a consistent reduction trend in newer generations (18.0–20.5 *versus* 6.7 per 1000 people born in 1960–1969 and in 1980–1989, respectively) [66–68]. The vast majority of these patients developed bronchiectasis following a lower respiratory tract infection in childhood (91–100%) [68].

In Canada, some case series of Inuit people suffering from primary ciliary dyskinesia (PCD) from the Qikiqtaaluk region have been described [69, 70]. In these patients, bronchiectasis was usually associated with neonatal respiratory distress, meconium aspiration, *situs inversus totalis*, chronic atelectasis, aspiration pneumonia, gastro-oesophageal reflux and chronic otitis and rhinitis [69, 70]. Based on these series, the estimated prevalence in Inuit people ranges between 70 and 202 per 100 000 children [69, 70].

Determinants of real epidemiological differences

The huge heterogeneity of epidemiological data on bronchiectasis could be the result of numerous factors, even beyond the methodological study limitations already mentioned so far. In this section, we aim to explore these potential determinants.

Aetiologies and associated conditions

Recently, the European bronchiectasis registry (European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC)) described the massive aetiological variation in European bronchiectasis patients, with over 15 different potential causes of the disease, the most common being idiopathic (38%) or post-infective (21%) [5]. Detection of underlying aetiologies is crucial for the related consequences in terms of clinical management and prognosis. Unfortunately, the local ability to perform a complete aetiological investigation can largely influence the aetiological classification of bronchiectasis and particularly the rate of idiopathic disease [71].

While the rarest causes of bronchiectasis show a similar prevalence rate across different European countries, most of the variability is linked to most common aetiologies. The rate of post-infective bronchiectasis is related to local healthcare access and it is often an investigator's assumption due to the absence of a previous negative CT scan [72]. In a similar way, the reported rates of bronchiectasis associated with COPD and asthma have also been extremely variable in the past, possibly due to differences in cohorts features and criteria used to define these associations [73]. Only recently has a consensus definition been published to define the association of COPD and bronchiectasis through the ROSE (radiology, obstruction, symptoms and exposure) criteria [74]. These criteria have identified a proper diagnosis of COPD as either an aetiology or a comorbidity in 19.6% of EMBARC patients, with a huge rate of misdiagnosis (>44%) [75]. Additionally, the prevalence of COPD varies enormously across countries, ranging between almost 60% in Macedonia and 5% in Sweden, likely according to local smoking habits. Unfortunately, the bad prognosis associated with comorbid COPD [34, 76–79] is likely to influence the distribution of the overall disease severity worldwide, defined through the bronchiectasis severity index (BSI). A similar study has described a 31% prevalence rate of asthma in EMBARC registry, but the lack of a standard definition and the poor application of asthma-specific tests (such as IgE and bronchodilation) makes this report a rough estimation that will need to be confirmed in the future, especially considering the potential therapeutic consequences [80]. Similarly, chronic rhinosinusitis has been classically described in association with bronchiectasis in 34–75% of cases and it is considered to contribute to disease activity as

potential source of airways inflammation and infection [73, 81]. Furthermore, this association seems to be based on an eosinophilic inflammatory pathway and could represent a differential phenotype of bronchiectasis [82].

Additionally, many comorbidities have been described in association with bronchiectasis, with variable rates depending on cohorts' demographics and healthcare systems, the most common being cardiovascular diseases (32.5% in EMBARC), anxiety and depression (14% each), osteoporosis (13%), and cancer (11%) [5]. Many of these can considerably contribute to the overall frailty of patients, severity scores and to the mortality risk [83]. Furthermore, beyond the possible causal relationship highlighted for some of them (such as rheumatic disorders or COPD [79]), most comorbidities are likely linked to bronchiectasis through shared inflammatory mediators [84]. For instance, the association between bronchiectasis and inflammatory bowel diseases influences the prognosis, as patients suffering from both conditions have a doubled mortality risk [83–85]. Finally, exposure to air pollution seems to play a role, as a Belgian cohort study identified a significant effect of living close to a major road on bronchiectasis patients' mortality [86].

Microbiology

Tuberculosis (TB) has been widely described as a possible aetiology of bronchiectasis. A systematic review recently highlighted that a significant proportion of patients previously treated for TB (35.0–86.0%) develops bronchiectasis at chest CT scan [87]. On the other hand, TB is recognised as the underlying aetiology of bronchiectasis in a variable proportion of patients according to the geographic area, ranging between the very low prevalence detected in Australia (1.8%) and the peaks detected in South Korea (20.1%) and India (35.5%) [7, 88, 89]. The estimated prevalence of post-TB bronchiectasis in the US and Taiwan are 4.0 and 12.4%, respectively [6, 90]. In Europe the overall prevalence is 4.9%, but geographical heterogeneity is consistent, as Moldova, Portugal and Turkey reach 20.2, 19.8 and 18.9%, respectively [5]. A description of post-TB bronchiectasis as a distinct phenotype has been proposed by some authors. FONG *et al.* [91] recently reported on a Singaporean cohort of bronchiectasis patients, in which patients with post-TB bronchiectasis had lower body mass index (BMI) and FEV₁, and a higher proportion of non-tuberculous mycobacteria (NTM) infections and haemoptysis during exacerbations. Furthermore, these patients showed an increased severity expressed through the FACED score and a shortened time to first exacerbation when compared to patients with bronchiectasis not associated with TB. These findings are partially confirmed by the Korean cohort described by CHOI *et al.* [92], in which patients suffering from post-TB bronchiectasis had a lower BMI, a more frequent association with COPD, an increased FACED severity and a higher rate of drug prescriptions, especially long-acting beta-agonists/long-acting muscarinic antagonists and mucolytics.

Infection from NTM is common in people suffering from bronchiectasis. Recent meta-analyses estimated a prevalence of NTM infection of about 10% in bronchiectasis patients, with consistent heterogeneity across studies [19, 93]. Although clinical and microbiological procedures may account for a part of this variability, a geographic effect is likely, as the proportion of people with at least one NTM isolation in North American (63%) and South Korean (25–44.5%) cohorts appears far higher than the ones reported in Italy (12.2–26.1%), Israel (8.6%), Spain (8.3%), Netherlands (5%), France (3.6%), Taiwan (3.6%) and Greece (0.9%) [6, 90, 94–102.] Regardless of whether NTM infection should be considered an aetiology or a consequence of bronchiectasis, a proportion of infected patients develops NTM pulmonary disease (NTM-PD) [103]. The “Lady Windermere” phenotype has been proposed in the past to describe elder, underweight women suffering from NTM-PD possibly related to sputum retention; however, similar features can be recognised in men [104, 105]. These patients tend to have lower BMI, inferior BSI and fewer exacerbations when compared to those with *P. aeruginosa* [96, 97]. On the other hand, healthcare costs associated with NTM management are remarkable [106]. Furthermore, NTM-PD seems to have an impact on mortality, as a Taiwanese matched-cohort study recently demonstrated that both single and multiple NTM isolates predict mortality after adjustment for multiple confounding factors [107].

Bronchiectasis and *Aspergillus* are partners in a complex relationship. From one side, exposure to environmental *Aspergillus fumigatus* can cause allergic bronchopulmonary aspergillosis (ABPA), another recognised aetiology for bronchiectasis. The prevalence of ABPA in the general population is estimated to be close to 4.8 million people worldwide, with a heavier burden in the US, China and India [5, 108]. In Europe, ABPA is far more common in Northern and Western countries when compared to Southern or Eastern countries [5]. *Aspergillus* species are ubiquitous moulds found in air and soil, but the reasons for such variability remain unclear and could possibly be explained through differences in either climate or the immunological properties of people living in different areas of the globe. On the other hand, *Aspergillus* can infect people with pre-existing lung conditions, including bronchiectasis, and lead to the development of chronic pulmonary aspergillosis (CPA) [109]. Despite being often unrecognised or considered a rare disease, CPA affects more than 6 million people worldwide, with a higher prevalence in low- and middle-income

countries. Furthermore, CPA has a considerable prognostic impact, yielding a 20% mortality in the year following the diagnosis and a 50% mortality in a 5-year period [110]. Finally, people suffering from CPA, and especially aspergilloma, have a high of experiencing haemoptysis and undergo hospitalisation.

P. aeruginosa is the most frequently isolated bacterial species in people suffering from bronchiectasis (25.1%, EMBARC) but with huge differences across countries, being markedly more frequent in Southern European countries compared to Northern-Western and Central-Eastern European countries [5]. Similarly, *P. aeruginosa* was detected in 13.7, 19.5 and 33% of patients enrolled in India, China and the US, respectively [6, 7, 42]. The prevalence of *P. aeruginosa* has direct consequences on the epidemiology of disease severity, since it is associated with increased mortality, exacerbations, economic burden and worsening lung function and quality of life [111–115]. However, in India *Enterobacterales* showed even a stronger association with mortality compared with *P. aeruginosa* (12.8% versus 6.8%) [44]. Consistently, other studies conducted in Europe and China did not find increased mortality in *Pseudomonas*-infected people after multivariate regression, suggesting that it might serve more as a disease severity marker than a prognostic factor [42, 116].

There is less data available on bacteria other than *Pseudomonas*. *Haemophilus (H.) influenzae* is the most frequently detected bacterium in most Northern European countries, including UK, while in other areas of the world seems to be rarer, with detection rates ranging between 0.5 and 9.2% [5–7, 90, 117]. Patients with *H. influenzae* chronic infection have a higher disease severity (BSI), a more extended radiological involvement and more exacerbations associated with an increase in outpatient morbidity [118–120]. However, the impact on hospital admissions, pulmonary function and mortality seems lower than *Pseudomonas* [119, 120]. Scarce information is available on chronic infection from *Staphylococcus (S.) aureus*, but data from the Spanish registry RIBRON suggest that it may more frequently affect younger, low-BMI people. Furthermore, chronic *S. aureus* infection seems to be associated with more exacerbations and faster functional decline when compared to people without chronic infections [121].

Access to care

Differences in access to care have a considerable impact on the epidemiology of bronchiectasis. Literature on this topic is very limited, especially from some areas of the globe (*i.e.* South America, Africa and Asia). Healthcare accessibility depends on several factors, including geographical, infrastructural, cultural, political and economic features of the explored region [122, 123]. Differences in access to care are particularly evident for low- and middle-income countries, especially between rural and urban areas [124], but can be manifest even in high-income countries, particularly concerning remote regions of large nations and minority groups [125, 126]. Figure 2 displays socioeconomic and healthcare-related factors potentially affecting epidemiology.

To begin with, the diagnosis of bronchiectasis requires high-resolution chest CT scan to be performed [1]. According to World Health Organization reports, the distribution of CT units varies between and within different regions worldwide: a median of 13.84 units per million (UPM) of inhabitants is reported in Europe, 7.23 in America (excluding USA with 44.56 UPM), 5.82 in Western-Pacific countries (excluding Australia, reporting 66.92 UPM), 3.82 in Eastern-Mediterranean countries, 1.51 in South-East Asia and 0.42 in Africa [127]. Data are unavailable for many areas, such as Central Asia. This unequal distribution can definitely preclude patients from being diagnosed and factitiously reduce bronchiectasis prevalence and incidence in areas with lower resources.

The latest European Respiratory Society (ERS) guidelines suggest performing a minimum bundle of aetiological tests (*i.e.* full blood cell count, immunoglobulin dosage and ABPA testing) in every bronchiectasis patient [3]. However, the application of this recommendation depends on the availability of laboratory tests in different contexts, with the risk of introducing the above-mentioned epidemiological bias related to “idiopathic” bronchiectasis [71]. Data about access to testing are extremely scarce. In Europe, few national audits investigated the aetiological workout applied in their country: immunoglobulins and ABPA were commonly assessed in Belgium and UK, while in Italy less than a quarter of patients were tested [128–130]. However, these data could not be applied to the present day, as British and Italian audits pre-date ERS guidelines. Another British audit focused on PCD recorded that only 2% of bronchiectasis patients underwent testing [131, 132]. Although international guidelines agree on limiting PCD testing to patients with high clinical suspicion, this could contribute to the underestimation of the disease [131]. In the US and Canada, healthcare and reimbursement issues complicate PCD diagnosis even further, as only 10% of affected individuals seem to receive a diagnosis and management in specialised centres [133]. Hence American Thoracic Society diagnostic guidelines slightly differ from ERS ones, facilitating large-scale diagnosis despite territorial and practical limitations [134, 135]. In Asia, a 2020 survey assessed

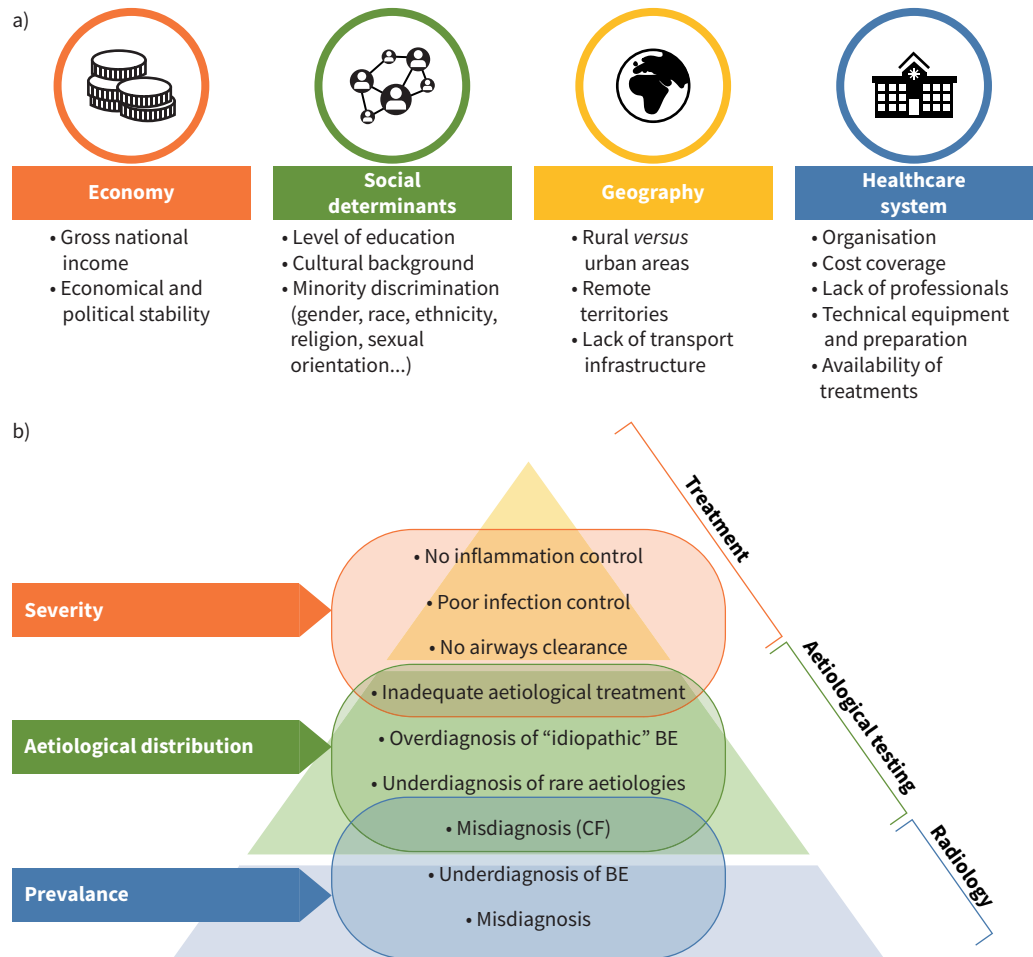


FIGURE 2 Causes and effects of unequal distribution to access to care in bronchiectasis. The first panel a) displays the main factors affecting patient’s access to healthcare facilities. The second panel b) depicts the effects on bronchiectasis epidemiology of unequal access to management, diagnostic resources and treatments. Access to lower tiers of the pyramid is mandatory to reach the higher ones. BE: bronchiectasis; CF: cystic fibrosis.

the application of international guidelines in Japan, South Korea, Singapore and Taiwan, demonstrating overall poor adherence [136]. In India, only 3.1% of patients enrolled in the national registry received a complete aetiological testing [7]. We could not find direct information regarding Australia and New Zealand, but evidence of diagnostic delay in patients with primary antibody deficiencies and bronchiectasis in these contexts might indirectly suggest underuse of immunoglobulin testing [137, 138]. Unfortunately, we found no information on South America, Africa, Middle East and the remaining part of Oceania. Details are available in table S1.

Up to date, pharmacological treatments have not been specifically approved for bronchiectasis in the US nor in Europe and most drugs are currently used off-label. Nevertheless, availability and correct applications of pharmacological treatments can potentially affect disease severity and prognosis. This is the case of inhaled antibiotics, recommended in selected cases by latest ERS guidelines [3]. Information about their accessibility is limited, as national drug regulatory agencies websites are often unavailable in English. Using an alternative approach based on research market reports, a list of countries with an inhaled antibiotic investor market was identified, as follows: three in North America, 10 in Europe, eight in Asia, one in Oceania, five in Africa and the Middle East, and two in South America [139]. Although this list may be incomplete, as it was obtained through unofficial sources, it may suggest that a consistent number of countries worldwide may not have access to inhaled antibiotics. Furthermore, drug availability is not the only limiting factor, since prescription, cost coverage and accessibility to administration devices also represent important challenges in some regions [140, 141]. Available data is reported in table S2. In the

EMBARC registry, long-term inhaled antibiotics were prescribed in 7.7% of patients, with consistent geographical variation between different European regions. For instance, 20% of Spanish patients receive this treatment, while in Italy only 1.1% do, despite similar geographical and socioeconomic features [5]. A part of this variability could be explained considering different rates of chronic bacterial infections, but this could also reflect difficulties in access to this treatment. In the US, patients treated with inhaled antibiotics reach 10% of the registry, while in India they only represent 3.6% of patients [7, 142]. Availability of inhaled antibiotics seem to be guaranteed in most centres in Singapore, although their effective use was not measured directly. Japanese, Taiwanese and Korean centres seem to rarely have access to this treatment [136]. Finally, Australian data suggest underuse of inhaled antibiotics, that were prescribed in half of the eligible patients according to guidelines [143].

Despite available evidence supporting pulmonary rehabilitation (PR) and airway clearance techniques (ACTs) and the interest expressed by patients, access to physiotherapy remains challenging due to several reasons [3, 144]. First, referral to PR specialists depends on awareness of the treating physicians [145]. Furthermore, availability of dedicated infrastructures, PR rehabilitation teams, economic sustainability and adaptability to certain cultural backgrounds represent possible limitations to patients' access in both high- and middle/low-income countries [146–148]. Significant differences in PR programmes for chronic respiratory conditions, including bronchiectasis, exist between Europe and the US [149]. In Europe, team expertise is more diversified, programmes usually include more patients and they are prevalently state-funded, while in the US GPs seem to be more likely to make referrals [149]. Attendance to PR/ACT programmes has also been reported to be very heterogeneous. In EMBARC, 51.5% of patients used ACT as part of their treatment [5]. This rate is significantly lower than the one reported in a UK survey (83%), but consistent with the one reported in the US registry (55.8%) [6, 150]. In the Indian registry, whilst 42% of patients had undergone ACT tuition, most eligible subjects missed out (62%) [7]. No publicly available data informs on the use of PR/ACT in the rest of Asia, but a survey reported that only half of the interviewed physicians from South Korea, Taiwan and Singapore regularly consider this treatment in bronchiectasis patients [136]. In Australia, most patients use ACT, while only 22% attended a PR programme despite 67% being eligible. Nonattendance was often due to an unspecified lack of referral [143]. Data from New Zealand are available only during exacerbations, when most patients (89%) received PR [151]. No data from South America and Africa is available. Implementation of new technologies, such as online videos or meetings, may assist in overcoming the barriers to referral by reaching people all over the world and decreasing the geographical differences limiting access to experienced physiotherapists [152]. However, this approach should not replace formal physiotherapy, nor distract both the medical community and patients from advocating access for each patient in need.

Conclusions

Overall, increasing prevalence and incidence rates of bronchiectasis have been described, potentially due to increasing disease awareness and advances in imaging techniques. Factors associated with increased prevalence seem to be female gender, socioeconomic deprivation and poor access to care. However, the ability to detect the disease seems to increase in presence of COPD or in case of screening protocols for cancer. In addition, a high socioeconomic burden has been broadly recognised worldwide in bronchiectasis, with main costs being related to hospitalisations, ICUs, antibiotics and loss of working days for both patients and caregivers.

Nevertheless, huge disparities in terms of disease epidemiology are still evident across different areas. Numerous are the potential determinants of the observed epidemiological variations in bronchiectasis. Relevant differences in geographical distribution of some pathogens have been described. This is the case for TB, NTM and *Aspergillus*-related conditions, which severely influence disease severity, treatment burden and healthcare costs across different regions. Among the usual pathogens, *P. aeruginosa* has also recently shown different prevalence rates and this can surely affect the overall disease severity, costs and outcomes. Both environmental factors and patients' immunological features could contribute to these variations, but still more research is needed to unravel this puzzle, as highlighted in table 3.

More importantly, socioeconomic deprivation and limited access to care can be considered major determinants of increased prevalence and mortality of bronchiectasis in some regions. This is the case of high-risk populations, such as Indigenous people from Australia and New Zealand or Inuit people from Canada. However, current data on availability of most relevant diagnostic tests or treatments suggest enormous inequalities in access to care all over the world. Additionally, appropriate detection of comorbidities and their management can affect disease severity and mortality risk as recently pointed out by EMBARC data.

TABLE 3 Research priorities related to the epidemiology of bronchiectasis

Research question	Related issues	Research perspectives to solve them
Which bronchiectasis definition should be used for epidemiological studies?	Several studies do not distinguish between the solitary radiological evidence of bronchiectasis and both clinically and radiologically significant bronchiectasis	A uniform, consensus-based definition of bronchiectasis for epidemiological studies
How should epidemiological data on bronchiectasis incidence, prevalence and mortality should be presented and analysed?	Different available data formats are hardly comparable	A uniform, consensus-based identification of the most appropriate way to present epidemiological data on bronchiectasis
What is the epidemiology of bronchiectasis in parts of the world not explored by currently available studies?	No data is available from highly populated areas of the globe, such as Africa, South America and the Middle East	More epidemiological, population-based studies in the unexplored areas Development of national and international registries in the aforementioned areas
How can reliable data on bronchiectasis-related mortality be obtained worldwide?	The mortality rate in bronchiectasis patients can vary according to aetiology, disease severity and activity, comorbidities, and access to medical care	More epidemiological, longitudinal long-term studies employing large-scale registries and real-world data with standardised diagnostic criteria
How does having comorbid asthma and/or COPD affect the epidemiology of bronchiectasis?	Do people with comorbid CADs have higher risk of developing bronchiectasis? The association of CAD with bronchiectasis can be chaotic and difficult to standardise at both national and international levels	A uniform, consensus-based definition of the criteria for the association between asthma and bronchiectasis Large-scale, population-based studies to explore incidence and prevalence of bronchiectasis, asthma, COPD and their association in the general population
How does microbiology affect the epidemiology of bronchiectasis?	Few data are available on the clinical implications and outcomes of patients suffering from chronic infections due to bacteria other than <i>Pseudomonas</i>	Studies describing specific characteristics of post-TB and ABPA-related bronchiectasis More epidemiological studies addressing the outcomes of people affected by chronic infections from bacteria different than <i>Pseudomonas</i> and NTM Large-scale studies to describe the true impact of <i>Pseudomonas</i> on the prognosis of bronchiectasis patients
How could differences in access to care be approached?	Disease awareness might be low in specific areas of the globe	Increasing patients and healthcare professionals' awareness of the disease Powering patient advocacy and requests for additional healthcare resources in specific areas of the globe Development of new drugs for bronchiectasis

ABPA: allergic bronchopulmonary aspergillosis; CAD: chronic airway disease; NTM: nontuberculous mycobacteria; TB: tuberculosis.

Certainly, more data is required from some regions such as South America, Africa and Asia, all underrepresented in the literature, to better understand the epidemiology and treatment gaps in the future.

Provenance: Commissioned article, peer reviewed.

Previous articles in this series: No. 1: Perea L, Faner R, Chalmers JD, *et al.* Pathophysiology and genomics of bronchiectasis. *Eur Respir Rev* 2024; 33: 240055. No. 2: Mac Aogáin M, Dicker AJ, Mertsch P, *et al.* Infection and the microbiome in bronchiectasis. *Eur Respir Rev* 2024; 33: 240038. No. 3: Van Braeckel E, Bosteels C. Growing from common ground: nontuberculous mycobacteria and bronchiectasis. *Eur Respir Rev* 2024; 33: 240058. No. 4: De Angelis A, Johnson ED, Sutharsan S, *et al.* Exacerbations of bronchiectasis. *Eur Respir Rev* 2024; 33: 240085. No. 5: Choi H, Xu J-F, Chotirmall SH, *et al.* Bronchiectasis in Asia: a review of current status and challenges. *Eur Respir Rev* 2024; 33: 240096.

Conflict of interest: M. Nigro, I.F. Laska and E. Simonetta have nothing to disclose. L. Traversi reports support for attending meetings from Chiesi, TEVA, Grifols and Pari. E. Polverino reports grants from Grifols, consultancy fees from Grifols, Insmmed, Chiesi, Pari, Electromed and AN2 Therapeutics, payment or honoraria for lectures, presentations, manuscript writing or educational events from Insmmed, TEVA, Chiesi and Pari, support for attending meetings from INSMED, and a leadership role with EMBARC (Co-Chair).

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