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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Dhar R, Singh S, Bronchiectasis in India: results from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) and Respiratory Research Network of India Registry D, et al. Title. *Lancet Glob Health* 2019; **7:** e1269–79.

Online supplement for:

Bronchiectasis in India: results from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) and Respiratory Research Network of India Registry

Supplementary methods—Radiology

For radiological scoring investigators entered their opinion as to which lobes were involved and the presence of cystic bronchiectasis into the online case report form system. Investigator assessments were validated by transmitting the CT images to the co-ordinating centre at the University of Dundee in the UK where the investigator assessment was verified. The Reiff score was then calculated centrally from the CT data as previously described—the modified Reiff score which awards points based on the severity of dilatation (1=cylindrical bronchiectasis, 2=varicose, 3=cystic, with points awarded for each lobe. The lingula was treated as a separate lobe resulting in a maximum score of 18 points).
Figure S1 below shows examples of some of the CT images uploaded

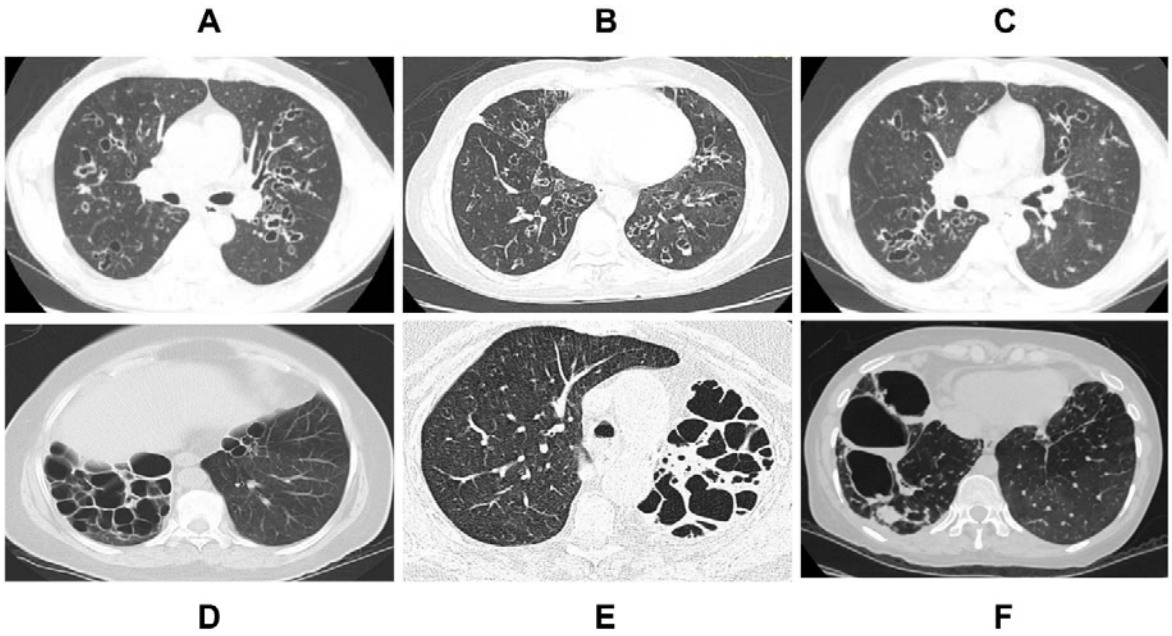

Figure S1. CT images from the EMBARC India registry from 6 randomly selected patients. Images A and B show predominantly cylindrical bronchiectasis. C demonstrates in addition varicose dilatation. D–F shows examples of severe cystic bronchiectasis representing the most frequently encountered imaging appearance found in this patient population.

Supplementary methods—Model selection

For the logistic regression models, multiple linear regression models and the negative binomial models variable selection was based on clinical relevance and published models as described in the online supplementary material. Data are presented as unadjusted and adjusted effect estimates for each covariate. Multicollinearity was evaluated using the variance inflation factor.

Online supplementary results

Table S1. Characteristics of the centres participating in the study

Site number	Site name	Tertiary vs secondary care	Approximate % urban vs rural population
1	Fortis Hospital - Kolkata, India.	Tertiary Care Hospital	70
2	Institute of Respiratory Disease, SMS Medical College, Jaipur, India.	Secondary Care Hodpital	40
3	Metro centre for Respiratory Diseases, India.	Tertiary Care Hospital	80
4	Mazumdar Shaw Medical Centre, Narayana Hrudayalaya, Bangalore, India.	Tertiary Care Hospital	60
5	King George's Medical University, Uttar Pradesh, India.	Secondary Care Hodpital	40
6	Getwell Hospital & Research Centre, Nagpur, India.	Tertiary Care Hospital	60
7	Jawaharlal Nehru Hospital & Research Centre, Bhilai, India.	Secondary Care Hodpital	70
8	PSG Institute of Pulmonary Medicine, Coimbatore, India.	Tertiary Care Hospital	70
9	St. John Medical College, Bengaluru, India.	Tertiary Care Hospital	40
10	Kerala Institute of Medical Sciences Trivandrum, India.	Secondary Care Hodpital	60
11	Kempegowda Institute of Medical Sciences, Bengaluru, India.	Secondary Care Hodpital	70
12	JSS Medical College, Mysuru, Karnataka, India.	Secondary Care Hodpital	40
13	Datta Meghe Institute of Medical Sciences Wardha, Maharashtra, India.	Secondary Care Hodpital	40
14	D.Y. Patil school of medicine, respiratory medicine, Navi Mumbai, India.	Secondary Care Hodpital	70
15	Jindal Clinics, Chandigarh, India.	Secondary Care Hodpital	90
16	MS Ramaiah Medical College, Bengaluru, India.	Secondary Care Hodpital	60
17	Govt. Multispecialty Hospital, Chandigarh, India.	Secondary Care Hodpital	40
18	Apollo hospitals, Guwahati, India.	Tertiary Care Hospital	40
19	Burdwan Medical College, Burdwan, India.	Secondary Care Hodpital	40

20	Sundaram Medical Foundation & SRM Institute of Medical Sciences, Chennai, India.	Secondary Care Hodpital	60
21	Galaxy Hospital Delhi and Yashoda Super speciality Hospital Kaushambi, Uttar Pradesh, India.	Secondary Care Hodpital	60
22	Unique Hospital Multispecialty & Research Centre, Surat, India.	Secondary Care Hodpital	80
23	Dhiraj hospital, Sumandeep University, Gujarat, India.	Secondary Care Hodpital	80
24	Pranayam Lung & Heart Institute and Research Centre, Vadodara, Gujarat, India.	Secondary Care Hodpital	80
25	All India Institute of Medical Sciences , Jodhpur, India.	Tertiary Care Hospital	40
26	Artemis Hospitals, Gurgaon, India.	Tertiary Care Hospital	80
27	Dr SN Medical College, Jodhpur, India.	Secondary Care Hodpital	40
28	Govt Medical College, Kerala, India.	Secondary Care Hodpital	40
29	Era & Lucknow Medical College & Hospital, Lucknow, India.	Tertiary Care Hospital	40
30	Deccan college of medical sciences, Hyderbad, India.	Secondary Care Hodpital	80
31	All India Institute of Medical Sciences Patna, Bihar, India.	Secondary Care Hodpital	20

Table S2. Daily sputum production

A logistic regression analysis was performed to identify ivariables associated with daily sputum production. Candidate variables were selected based on biological plausibility and clinical importance. In the table below an odds ratio below 1 indicates a negative association with dry bronchiectasis, while an odds ratio above 1 indicates that patients are more likely to be non-sputum producers. The odds ratios presented below are adjusted odds ratios. The statistically significant variables associated with sputum production were PPI use, FEV1, COPD, MRC dyspnoea score, frequency of exacerbations, *P. aeruginosa* infection, cystic bronchiectasis and inhaled corticosteroid use. Variables associated with the absence of sputum production were rhinosinusitis, idiopathic or post-infective bronchiectasis and macrolide therapy. Multicollinearity was evaluated and none of the VIF values were greater than 5. This suggests that patients with more severe bronchiectasis are more likely to be sputum producers. The association of rhinosinusitis with lack of sputum production is unexplained. The finding that macrolide therapy is associated with lack of sputum production may relates to successful treatment e.g patients may have been sputum producers prior to the initiation of treatment. Macrolides have been shown to reduce sputum volume in randomized controlled trials. It should be noted that the absence of daily

sputum production is not synonymous with “dry bronchiectasis” since patients may still produce sputum intermittently.

Clinical and demographic features	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	P-value (adjusted)
Age	1.0 (0.99-1.01)	2.0 (0.99-1.01)	0.71
Gender	0.83 (0.70-0.99)	0.94 (0.76-1.15)	0.50
Cardiovascular disease	0.80 (0.63-1.01)	1.14 (0.88-1.49)	0.35
Proton pump inhibitor use	0.61 (0.51-0.73)	0.78 (0.63-0.96)	0.027
FEV_1 >80% predicted	1.00 (reference)	1.00 (reference)	
FEV_1 50-79% predicted	1.03 (0.82-1.31)	1.10 (0.85-1.43)	0.55
FEV_1 30-49% predicted	0.64 (0.49-0.84)	0.81 (0.61-1.09)	0.23
FEV_1 <30% predicted	0.45 (0.30-0.68)	0.58 (0.38-0.91)	0.022
Asthma	1.15 (0.93-1.40)	0.95 (0.74-1.24)	0.78
COPD	0.46 (0.37-0.57)	0.63 (0.48-0.82)	0.016
Modified MRC dyspnoea score	0.66 (0.61-0.71)	0.79 (0.72-0.87)	<0.0001
Rhinosinusitis	1.40 (1.07-1.81)	1.48 (1.10-2.00)	0.0098
Never smoker	1.00 (reference)	1.00 (reference)	
Ex-smoker	0.65 (0.53-0.81)	0.94 (0.72-1.22)	0.66
Current smoker	0.70 (0.47-1.05)	1.03 (0.65-1.61)	0.94
Exacerbation frequency	0.85 (0.81-0.90)	0.92 (0.87-0.97)	0.0021
Aetiology			
- Post TB	1.0 (reference)	1.0 (reference)	
- Idiopathic	1.49 (1.19-1.89)	1.42 (1.10-1.83)	0.0072
- Post-infective	1.30 (1.03-1.63)	1.33 (1.03-1.70)	0.035
- ABPA	1.43 (1.04-1.95)	1.25 (0.85-1.83)	0.33
- Others	0.87 (0.49-1.56)	1.00 (0.72-1.40)	0.98
P. aeruginosa infection	0.40 (0.31-0.53)	0.48 (0.36-0.64)	<0.0001
Radiological severity			
- Cylindrical	1.0 (reference)	1.0 (reference)	
- Varicose	1.16 (0.78-1.73)	1.42 (0.93-2.18)	0.12
- Cystic	0.69 (0.57-0.83)	0.74 (0.60-0.91)	0.0048
Inhaled corticosteroid treatment	0.72 (0.60-0.86)	0.81 (0.67-0.99)	0.044
Macrolide treatment	1.41 (1.00-2.01)	2.06 (1.39-3.04)	<0.0001

Table S2. Logistic regression of factors associated with lack of sputum production on a daily basis

Table S3. The frequent exacerbator phenotype

A comparison between frequent exacerbators, defined as experiencing 3 or more per year, and non-frequent exacerbators is shown in the table below. Patients with frequent exacerbations had a higher frequency of some co-morbidities (notably GORD), more severe bronchiectasis using the bronchiectasis severity index, worse radiological disease, higher sputum volumes, worse lung function, more bacterial infection and worse quality of life.

Variables		Non-frequent exacerbators	Frequent exacerbators
n.		1666	529
Demographics			
Median (IQR) age, years		56 (42-66)	56 (42-66)
Male, n (%)		917 (55.0%)	332 (62.8%)
Median (IQR) BMI,		21.7 (18.9-24.7)	21.0 (17.6-23.9)
Ex smokers, n (%)		372 (22.3%)	134 (25.3%)
Current smokers, n (%)		72 (4.3%)	41 (7.8%)
Comorbidity			
Ischaemic heart disease, n (%)		255 (15.3%)	100 (18.9%)
Stroke, n (%)		7 (0.4%)	2 (0.4%)
Diabetes, n (%)		232 (13.9%)	83 (15.7%)
Liver disease, n (%)		8 (0.5%)	10 (1.9%)
Chronic renal failure, n (%)		16 (1.0%)	10 (1.9%)
COPD, n (%)		365 (21.9%)	147 (27.8%)
Asthma, n (%)		372 (22.3%)	113 (21.4%)
Osteoporosis, n (%)		94 (5.6%)	36 (6.8%)
GERD, n (%)		221 (13.3%)	125 (23.6%)
Solid tumor, n (%)		13 (0.8%)	4 (0.8%)
Disease severity			
Median (IQR) BSI score,		5 (3-8)	10 (8-13)
BSI score Risk Class, n (%)	Mild	712 (42.7%)	16 (3.0%)
	Moderate	548 (32.9%)	126 (23.8%)
	Severe	406 (24.4%)	387 (73.2%)
Radiological status			
Median (IQR) Reiff score		6 (3-9)	6 (4-10)
% cystic dilatation		1014 (60.9%)	376 (71.1%)
Clinical status			
Sputum volume ml/day		5 (0-25)	20 (0-50)
MRC, median (IQR)		1 (1-2)	2 (2-3)
Median (IQR) exacerbations in the previous year		1 (0-2)	4 (3-5)
at least one hospitalization in the previous year, n (%)		451 (27.1%)	400 (75.6%)
Functional Status			
Median (IQR) FEV_1 % predicted		52.7 (368-67.9)	47.4 (31.2-62.9)
Microbiology			
P. aeruginosa, n (%)		188 (11.3%)	113 (21.4%)
H. influenzae, n (%)		8 (0.5%)	3 (0.6%)
S. aureus, n (%)		33 (2.0%)	17 (3.2%)
M. catarrhalis, n (%)		19 (1.1%)	3 (0.6%)
Enterobacteriaceae, n (%)		138 (8.3%)	77 (14.6%)
Treatment			
Long term macrolide treatment, n (%)		70 (4.2%)	64 (12.1%)
Other long term oral antibiotics treatment, n (%)		106 (6.4%)	31 (5.9%)
Inhaled antibiotic treatment, n (%)		39 (2.3%)	40 (7.6%)

Quality of life		
Quality of life bronchiectasis questionnaire Respiratory Symptom Score	66.7 (53.7-77.8)	51.9 (39.8-63.0)

Table S3. Comparison of frequent and infrequent exacerbators.

Table S4. Low FVC (Spirometric restriction)

The spirometric pattern demonstrates an FVC less than 80% of predicted value and FEV1/FVC ratio greater than 0.7 was explored using multiple logistic regression to determine associations with clinical parameters. In this analysis we observed a strong association between this low FVC phenotype and history of pulmonary tuberculosis – Odds ratio 2.02 95% CI 1.45-2.82,p<0.0001. The table below shows other characteristics associated with low FVC. Multicollinearity was evaluated and none of the VIF values were greater than 5.
In the table below, an association greater than 1.0 indicates a higher likelihood of being in the low FVC group. Therefore younger age, female sex, post-TB or post-infective aetiology, infection with enterobacteriaceae and a lower MRC dyspnoea score. The latter likely reflects an association between MRC dyspnoea score and airflow obstruction.

Clinical and demographic features	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Adjusted p-value

Age	0.99 (0.98-0.99)	0.99 (0.98-0.99)	<0.0001
Male sex	0.74 (0.62-0.88)	0.77 (0.62-0.94)	0.013
Cardiovascular disease	0.69 (0.64-0.88)	0.90 (0.68-1.19)	0.51
Diabetes	1.03 (0.80-1.32)	1.21 (0.91-1.59)	0.27
Proton pump inhibitor use	0.84 (0.70-1.01)	1.08 (0.87-1.33)	0.58
BMI	0.99 (0.97-1.01)	0.99 (0.97-1.01)	0.44
Asthma	0.90 (0.73-1.12)	1.06 (0.82-1.37)	0.71
Rhinosinusitis	0.84 (0.64-1.12)	0.85 (0.62-1.15)	0.36
Daily sputum production	1.23 (1.03-1.46)	1.14 (0.94-1.39)	0.20
Modified MRC dyspnoea score	0.85 (0.79-0.92)	0.85 (0.79-0.92)	<0.0001
Never smoker	1.0 (reference)	1.0 (reference)	
Ex-smoker	0.73 (0.59-0.91)	0.90 (0.69-1.17)	0.42
Current smoker	0.99 (0.66-1.47)	1.05 (0.68-1.62)	0.88
Exacerbation frequency	0.97 (0.93-1.01)	0.98 (0.94-1.03)	0.56
Aetiology			
- Post TB	2.13 (1.55-2.92)	2.02 (1.45-2.82)	<0.0001
- Idiopathic	1.34 (0.95-1.89)	1.21 (0.84-1.73)	0.35
- Post-infective	1.83 (1.31-2.56)	1.69 (1.18-2.40)	0.0049
- ABPA	1.22 (0.80-1.85)	0.97 (0.61-1.53)	0.93
- Others	1.00 (reference)	1.00 (reference)	
P. aeruginosa infection	0.91 (0.71-1.18)	0.99 (0.76-1.30)	0.96
Enterobacteriaceae infection	1.38 (1.04-1.84)	1.53 (1.12-2.07)	0.0072
Lobes involved on CT	0.97 (0.95-0.99)	0.97 (0.94-0.99)	0.045
Radiological severity			
- Cylindrical	1.0 (reference)	1.0 (reference)	
- Varicose	0.98 (0.65-1.48)	1.09 (0.70-1.68)	0.72
- Cystic	0.88 (0.73-1.07)	1.12 (0.87-1.45)	0.40
Inhaled corticosteroid treatment	0.87 (0.73-1.04)	0.99 (0.81-1.21)	0.95
Macrolide treatment	1.00 (0.70-1.45)	1.02 (0.69-1.51)	0.92

Table S4. Logistic regression analysis of factors associated with the low FVC (spirometric restriction) phenotype.

Table S5. Negative binomial model for exacerbation frequency

The model below shows the adjusted incident rate ratios derived from a negative binomial model. The outcome was exacerbations during the study with duration of observation as an offset. The variables selected for the model were determined apriori based on published models for exacerbation prediction and those variables that were frequent and thought to be potential modifiers of exacerbation risk within the Indian dataset. Obviously collinear variables were excluded a-priori, therefore for example COPD and FEV1 were not entered into the same model. The variables significantly associated with increased exacerbations included male sex, *P. aeruginosa* infection, daily sputum production, higher MRC dyspnoea score, worse radiological severity using the Reiff score, use of macrolide antibiotics and bronchiectasis associated with a history of pulmonary tuberculosis. The association between macrolides and increased frequency of exacerbations is likely to represent bias by indication, i.e that macrolides are prescribed to patients experiencing more exacerbations, rather than being causal.

Clinical and demographic features	Unadjusted incident rate ratio (95% CI)	Adjusted incident rate ratio (95% CI)	Adjusted P-value
Age	1.0 (0.99-1.00)	1.00(0.99-1.00)	0.81
History of pulmonary TB	1.19 (1.07-1.32)	1.20 (1.07-1.34)	0.002
Male sex	1.16 (1.05-1.30)	1.17 (1.03-1.32)	0.015
P. aeruginosa infection	1.57 (1.36-1.82)	1.29 (1.10-1.50)	0.001
Enterobacteriaceae infection	1.33 (1.12-1.58)	1.13 (0.94-1.35)	0.19
H. influenzae infection	1.01 (0.48-2.13)	1.21 (0.57-2.59)	0.62
Diabetes	1.16 (1.00-1.34)	1.08 (0.92-1.27)	0.34
Cardiovascular comorbidity	1.13 (0.98-1.30)	0.95 (0.82-1.11)	0.95
Gastrooesophageal reflux disease	1.27 (1.11-1.47)	1.15 (0.99-1.33)	0.073
FEV1 >80% predicted	1.0 (reference)	1.00 (reference)	
FEV1 50-80% predicted	0.98 (0.85-1.14)	1.06 (0.90-1.24)	0.48
FEV1 30-49% predicted	1.17 (0.99-1.37)	1.06 (0.89-1.25)	0.52
FEV1 0-29% predicted	1.31 (1.05-1.65)	1.00 (0.79-1.27)	0.98
Reiff score (radiological severity)	1.05 (1.04-1.06)	1.03 (1.01-1.04)	<0.0001
Daily sputum production	1.43 (1.28-1.59)	1.16 (1.03-1.30)	0.013
MRC dyspnoea score	1.39 (1.33-1.46)	1.32 (1.25-1.39)	<0.0001
Smoking- never smoker	1.00 (reference)	1.00 (reference)	
Smoking- ex smoker	1.12 (0.98-1.26)	0.89 (0.77-1.04)	0.14
Smoking – current smoker	1.31 (1.04-1.66)	1.05 (0.82-1.35)	0.70
Inhaled corticosteroid treatment	1.20 (1.08-1.34)	1.05 (0.93-1.18)	0.42
Macrolide treatment	1.63 (1.33-2.00)	1.48 (1.19-1.83)	<0.0001

Table S5. Negative binomial model of predictors of exacerbations. Data are presented as adjusted incident rate ratios.

Table S6. Quality of life

The quality of life bronchiectasis questionnaire was used to evaluate quality of life. The respiratory symptoms scale is the most widely used in clinical practice and so this is the scale evaluated below. A multiple linear regression analysis was used to identify factors associated with quality of life using this questionnaire. As above, the variables included were determined a-priori based on clinical relevance. The adjusted effect estimates are shown in Table S2. The resulting model explained 61% of the variance in quality of life. The independent variables associated with quality of life in the Indian context were MRC dyspnoea score, sputum volume, frequency of exacerbations and enterobactericeae infection. The total results are shown below.

Clinical and demographic features	Unadjusted effect estimate (95% CI)	Adjusted effect estimate (95% CI)	P-value
Age	-0.5 (-0.2, 0.1)	0.2 (-0.1, 0.2)	0.84
Gender	0.6 (-4.4, 5.5)	-0.5 (-5.0, 3.9)	0.85
Cardiovascular disease	-4.9 (-10.1, 0.3)	-1.1 (-5.8, 3.6)	0.62
Proton pump inhibitor use	-1.7 (-6.9, 3.5)	-2.4 (-7.7, 2.9)	0.47
Diabetes	-3.1 (-11.5, 5.3)	-2.5 (-9.8, 4.7)	0.56
FEV_1	1.0 (0.1, 0.2)	0.7 (-1.2, 2.5)	0.50
Asthma	-0.1 (-5.6, 5.3)	-1.8 (-6.8, 3.1)	0.56
COPD	-3.8 (-9.0, 1.3)	-1.3 (-6.1, 3.5)	0.64
Modified MRC dyspnoea score	-8.1 (-10.2, -6.0)	-5.8 (-8.1, -3.5)	<0.0001
Sputum volume (per 10ml)	-2.3 (-1.6, -2.9)	-1.4 (-2.1, - 7.1)	<0.0001
Exacerbation frequency	-2.3 (-3.2, -1.4)	-1.0 (-1.9, -0.9)	0.035
Aetiology	-0.4 (-1.3, 0.5)	-0.2 (-1.7, 1.4)	0.81
P. aeruginosa infection	-8.5 (-14.4, -2.6)	-3.8 (-9.3, 1.7)	0.25
Enterobacteriaceae infection	-15.6 (-23.5, -7.8)	-11.6 (-18.5, -4.7)	0.0014
Reiff Radiological severity score	-0.6 (-1.1, -0.1)	- 1.6 (-4.2, 1.1)	0.23
Inhaled corticosteroid treatment	-3.6 (-9.8, 2.6)	-1.1 (-7.0, 4.9)	0.70
Macrolide treatment	-1.9 (-12.8, 9.0)	-5.8 (-15.6, 4.0)	0.21

Table S6. Multiple linear regression analysis of factors associated with quality of life bronchiectasis questionnaire respiratory symptom score.(QOL-B-RSS)

Figure S2. Comparison of the microbiology in different geographical regions

The figure below shows a comparison of the patients enrolled in the Indian, European and US bronchiectasis Registries. The % of each organism is provided as a percentage of those individuals with samples taken, as the microbiology of patients who did not provide sputum samples cannot be determined.

The results show a higher frequency of NTM in the US registry, and *H. influenzae* in the European registry while *P. aeruginosa* is the organism with the most consistent frequency throughout each of the registries.

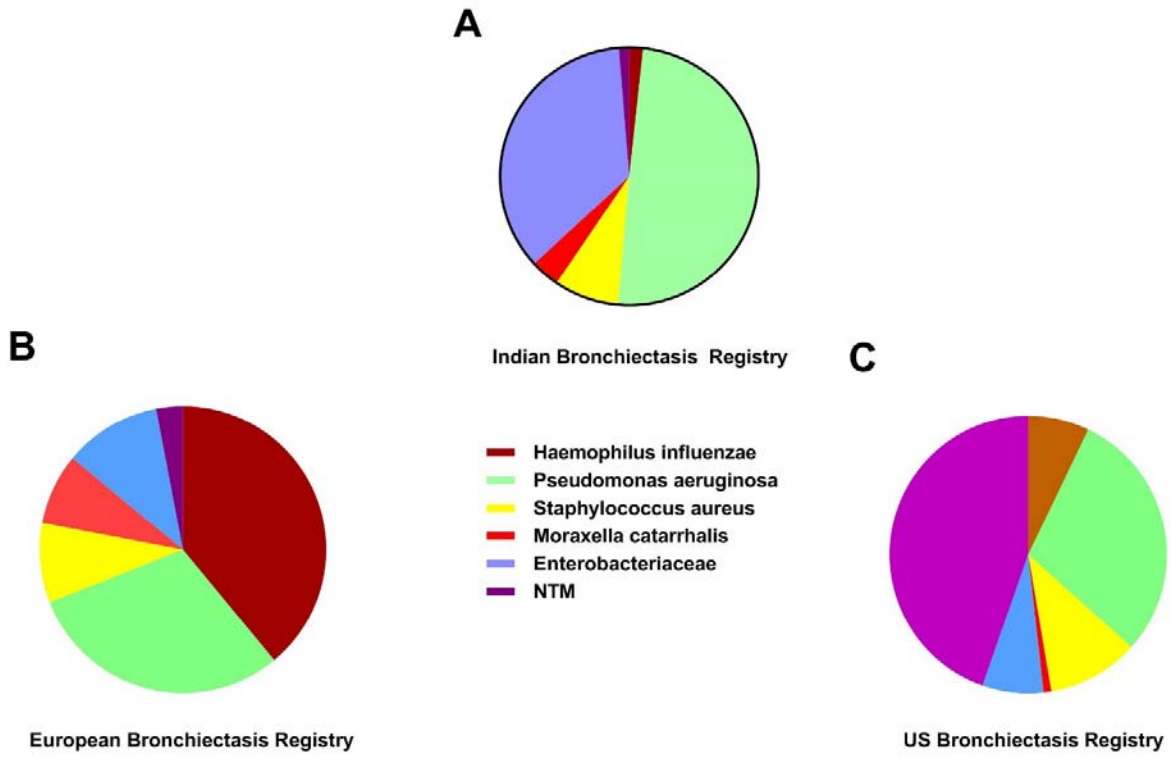

Figure S2. A: Indian bronchiectasis registry microbiology. B: European Bronchiectasis Registry microbiology, C: US bronchiectasis registry microbiology.