The global impact of *Aspergillus* infection on COPD

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Introduction

- Chronic obstructive pulmonary disease (COPD) is the most prevalent non-communicable disease of the lungs. It is progressive and irreversible with associated mortality highest in less-developed countries.
- An ageing population has led to a recent relative increase in the global burden of COPD mortality, highlighting COPD as a significant global health concern.
- The strongest risk factors for COPD are smoking and indoor exposure to biomass; other factors include family history, genetics including alpha-1-antitrypsin deficiency, age, education, tuberculosis, and occupational exposures.
- Bacteria and viruses are a major cause of COPD exacerbations whereas the role of fungi is less well understood.
- *Aspergillus*, a ubiquitous soil-dwelling fungi, is the most common cause of a range of pulmonary fungal conditions including invasive aspergillosis (IA), chronic pulmonary aspergillosis (CPA) and allergic bronchopulmonary aspergillosis (ABPA).
- IA is almost always fatal if not identified and treated early. COPD is one of many underlying risk factors for IA, including neutropenia, liver disease, diabetes mellitus, AIDS, and those on immunosuppressive treatment.
- Prior estimates of the annual global incidence of IA range from 200,000, but difficulties in the precise diagnosis of IA in COPD patients has restrained efforts to include this group in the estimates.

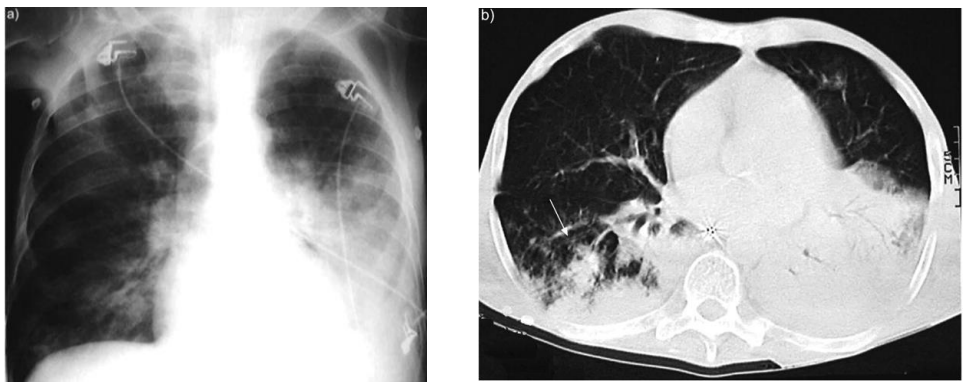

Figure 1. *Invasive aspergillosis present in a patient with COPD visualised by a) chest radiograph, b) computed tomography scan of the thorax (Bulpa P et al Eur Resp J 2007;30:782).*

Aims

- Provide global and individual country estimates for COPD.
- Estimate the annual incidence of cases of IA in COPD patients and likely associated mortality.
- Assess whether *Aspergillus* sensitisation contributes to the severity of COPD.

Methods

- A systematic review of COPD prevalence using PRISMA guidelines was undertaken, and estimates derived by country and globally.
- GOLD criteria for grade II, III or IV (FEV_1/FVC <70% and FEV_1 <80%) using spirometry were used.
- Given limited data, a conservative 10.5% estimate of COPD patients hospitalised annually was assumed based on studies in Algeria.
- A separate literature search assessed the impact of *Aspergillus* sensitisation on severity of COPD (by FEV_1).
- Hospitalised COPD patients develop IA in 1.3% - 3.9% of cases, based on positive cultures of *Aspergillus spp*. and radiological findings. Mortality was estimated based on the diagnosis of IA being made and patients treated.

GOLD grading	Diagnostic criteria
GOLD grade I (mild)	FEV_1 ≥80% of predicted value
GOLD grade II (moderate)	FEV_1 50-79% of predicted value
GOLD grade III (severe)	FEV_1 30-49% of predicted value
GOLD grade IV (very severe)	FEV_1 <30% of predicted value

Table 1. *GOLD classification of COPD severity (i.e. severity of airflow limitation) in patients with FEV_1/FVC ratio <0.70.*

Results

Country	Population size	COPD population GOLD stages II-IV n (% of population)	COPD annual hospitalisation rate 10.50% of COPD population	IA annual rate 1.30 - 3.90% of COPD hospitalisation rate		IA mortality rate n (% of IA cases)	
Africa	1,197,415,000	64,298,051	6,751,295	87,767	1.30%	62,929	71.70%
				271,877	3.90%	115,996	43.00%
America	1,001,386,000	85,278,783	8,954,272	1164,06	1.30%	834,63	71.70%
				349,217	3.90%	150,163	43.00%
Asia	4,476,519,000	339,206,893	35,616,724	462,894	1.30%	331,895	71.70%
				1,389,052	3.90%	597,292	43.00%
Europe	765,958,000	59,484,329	6,245,855	81,196	1.30%	58,218	71.70%
				247,744	3.90%	106,530	43.00%
Oceania	37,131,000	4,032,543	423,417	5,504	1.30%	3,947	71.70%
				16,513	3.90%	7,101	43.00%
Globally	**7,478,409,000**	**552,300,599**	**57,991,563**	**753,767**	**1.30%**	**540,451**	**71.70%**
				2,274,403	**3.90%**	**977,082**	**43.00%**

Table 2. *A summary by continent and an overall global estimate of COPD prevalence, hospitalisation rate, IA prevalence in COPD and associated mortality.*

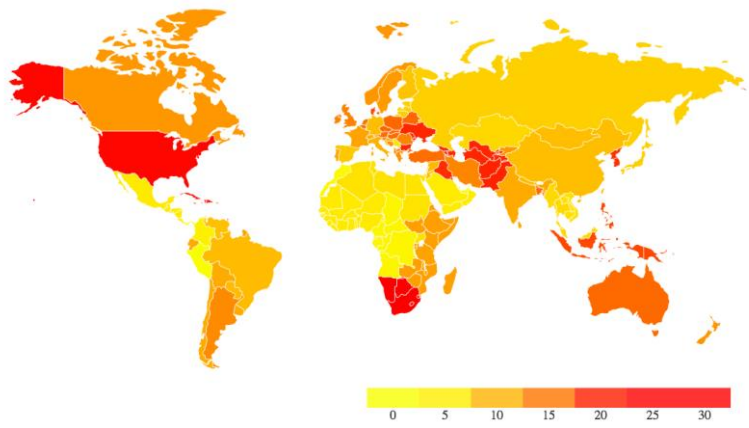

Figure 2. *Estimated global incidence of invasive aspergillosis (IA) per 100,000 population, assuming the lower estimate of 1.3% of hospitalised COPD patients having IA. Countries with populations <1 million were not estimated and are in white.*

Location, author, year	Sensitised to *Aspergillus*, %		No. of patients
	Control	COPD	
China, Jin et al, 2014	-	15.0	273
Belgium, Everaerts et al, 2017	4.0	18.3	300
India, Agarwal et al, 2010	0.0	8.5	200
United Kingdom, Bafadhel et al, 2014	-	13.0	128
Colombia, Le Pape et al, 2018	-	7.9	127
Weighted average:	**2.4**	**13.6**	**Total: 1028**

Table 3. *Prevalence of Aspergillus sensitisation in patients with COPD.*

Author, year	FEV_1 % of predicted		Number of patients
	Sensitised	Non-sensitised	
Jin et al, 2014	37	41	142
Everaerts et al, 2017	41	43	300
Agarwal et al, 2010	52.9	48.9	200
Bafadhel, 2014	39	51	128
Weighted average (weighted SD):	**43.0 (7.0)**	**45.5 (4.6)**	**Total: 770**

Table 4. *Comparison of FEV1 between sensitised and non-sensitised patients with COPD 7.0-18.3% (weighted mean 13.6%).*

Conclusion

- Global estimate of COPD calculated to be 552,300,599 cases compared to existing estimate of 251 million reported by the Global Burden of Disease Study in 2016.
- An estimated 57,991,563 patients are hospitalised annually worldwide due to COPD – this is thought to be underestimated given limited data available and number of hospitalisations relating to COPD severity.
- Global IA incidence was estimated to be between 753,767 - 2,274,403 annually, with an associated mortality rate between 540,451 - 977,082 per year.
- Overall *Aspergillus* sensitization was found to lower FEV_1 by 2.5% (statistically insignificant) and was therefore shown to not significantly impact the severity of COPD in these patients.

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