

# CHRONIC PULMONARY ASPERGILLOSIS IN TUBERCULOSIS



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# What is Chronic Pulmonary Aspergillosis<sup>1</sup>?

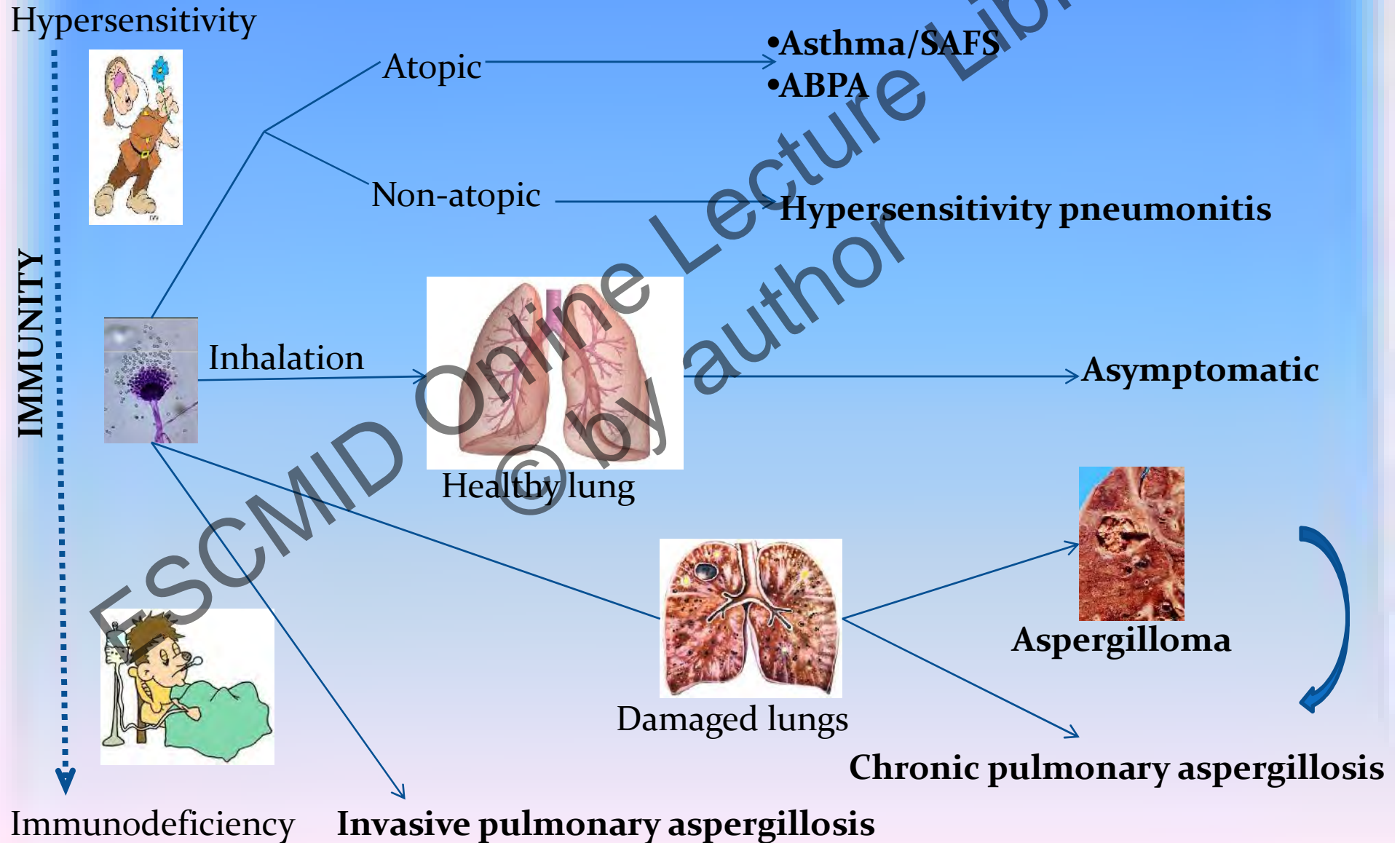
- *Confusion!*
- Syn.
  - pulmonary aspergillosis with cavitation
  - complex aspergilloma
  - symptomatic aspergilloma
  - Aspergillus pseudotuberculosis
  - chronic granulomatous aspergillosis
  - CNPA<sup>2</sup>
  - Semi-invasive pulmonary aspergillosis<sup>3</sup>
- The stage between colonization and invasive pulmonary aspergillosis

<sup>1</sup>Schiraldi GF et al. Curr Opin Investig Drugs. 2003;4:186-91.

<sup>2</sup>Binder et al. Medicine 1982;61:109-24.

<sup>3</sup>Geffer WB. J Thorac Imaging. 1992;7:56-74.

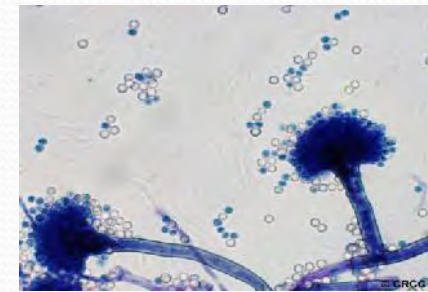
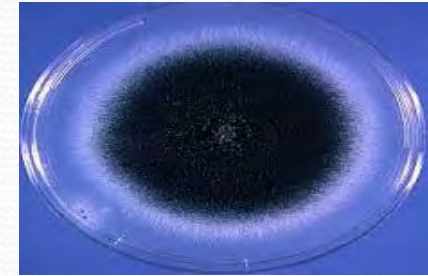
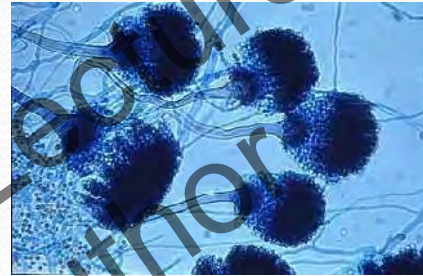
# Spectrum of pulmonary aspergillosis





# What is CPA caused by?

- *Aspergillus* spp.
  - *Aspergillus fumigatus*
  - *A. flavus*
  - *A. niger*
  - *A. terreus*
  - *A. nidulans*



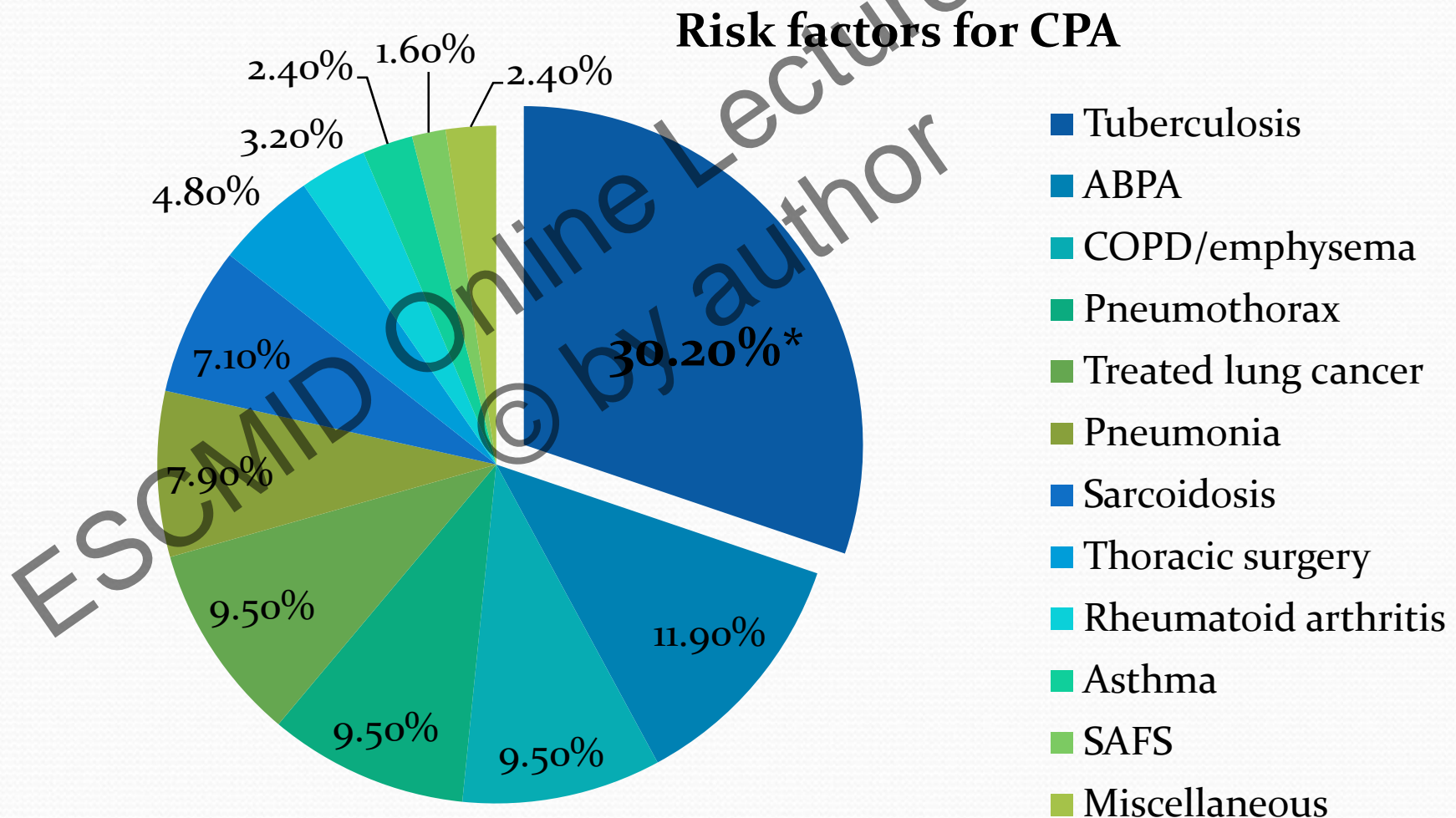
Longbottom JL et al. *Lancet* 1964;1:588-9.  
Severo LC et al. *Rev Iberoam Micol* 1997;14:104-10.  
Pasqualotto AC, Denning DW. *Med Mycol* 2008;46:275-8.

# Who gets chronic pulmonary aspergillosis?

- Men > Women; middle-aged to elderly
- Immune status ranging from normal to mild immunosuppression
- Those with risk factors
  - Pre-existing lung damage
    - **Mycobacterial lung infection**, *Legionella* infection
    - Emphysema, bullae, asthma, sarcoidosis, pneumoconiosis, lung cancer, thoracic surgery, upper lobe fibrosis
  - Defects in innate immunity
  - Diabetes mellitus
  - Corticosteroid use
  - Alcohol abuse
  - AIDS

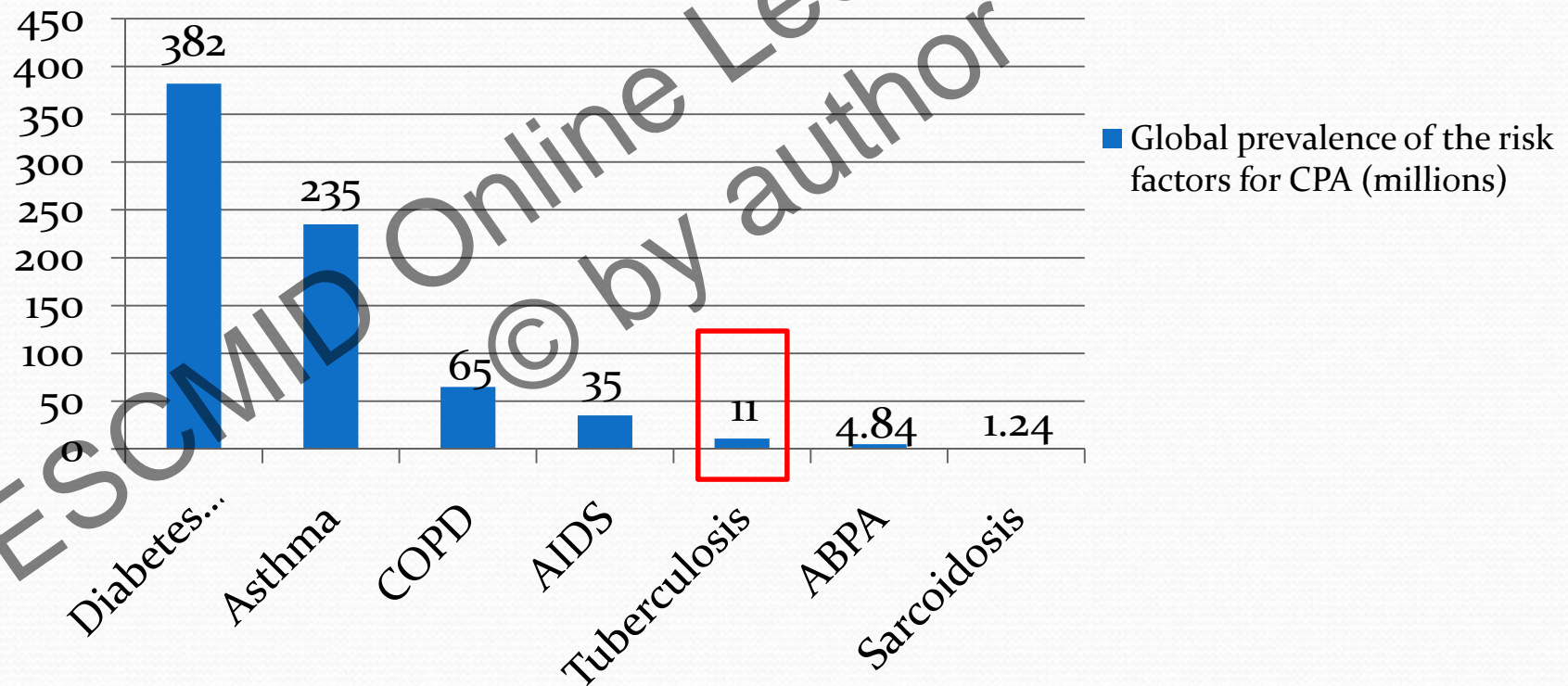


# What are the risk factors for CPA?



# How common are these risk factors?

Global prevalence of the risk factors for CPA  
(millions)



How important is TB for CPA?

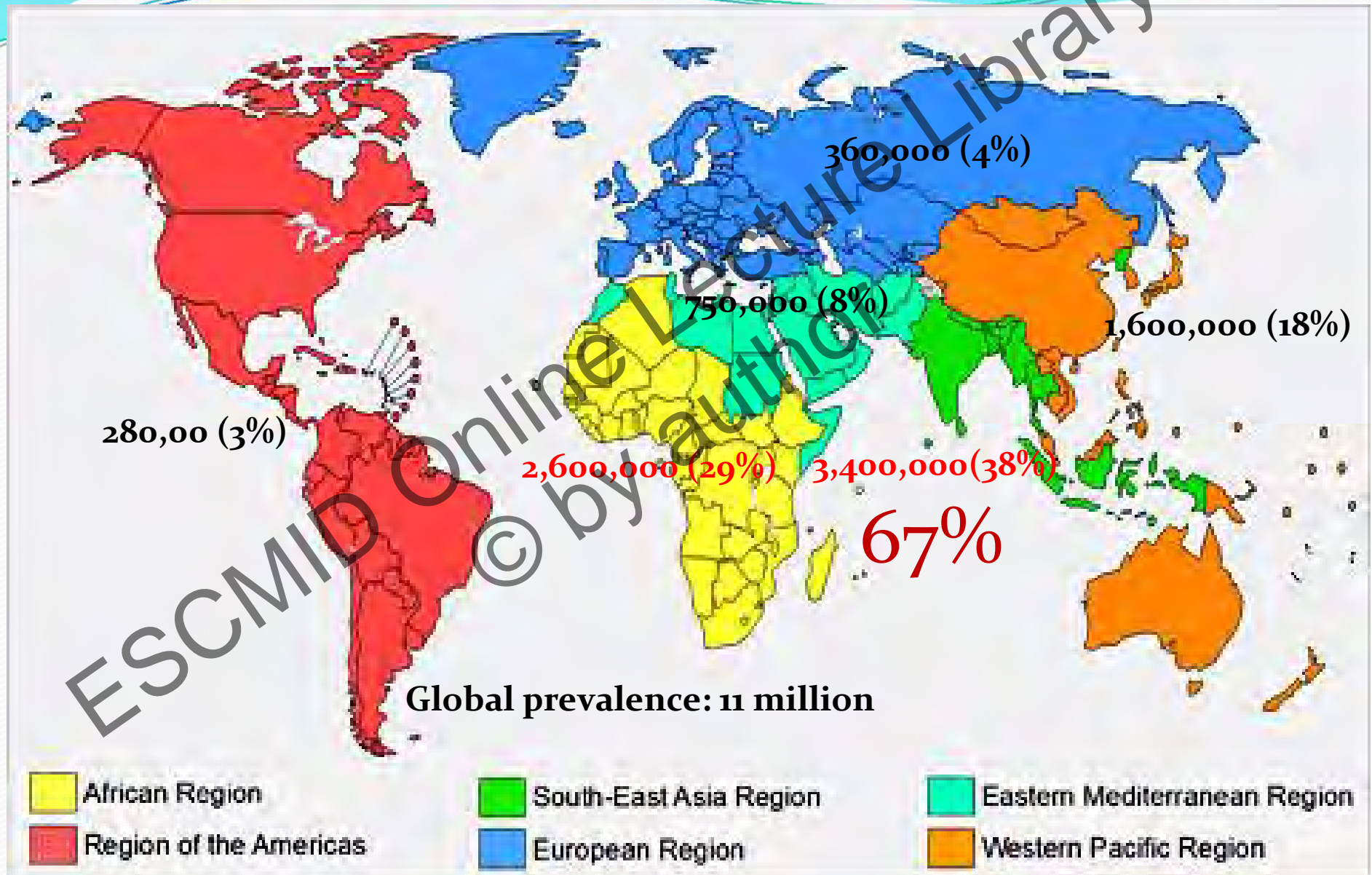
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# Epidemiological coherence

- **Demographics of TB (2013-14)**
  - Prevalence: 11 million
  - Incidence: 9 million
  - Maximum burden: Asia and Africa (65%)
    - India + China: 3 million (33%)
    - India : 2.1 million (24%)

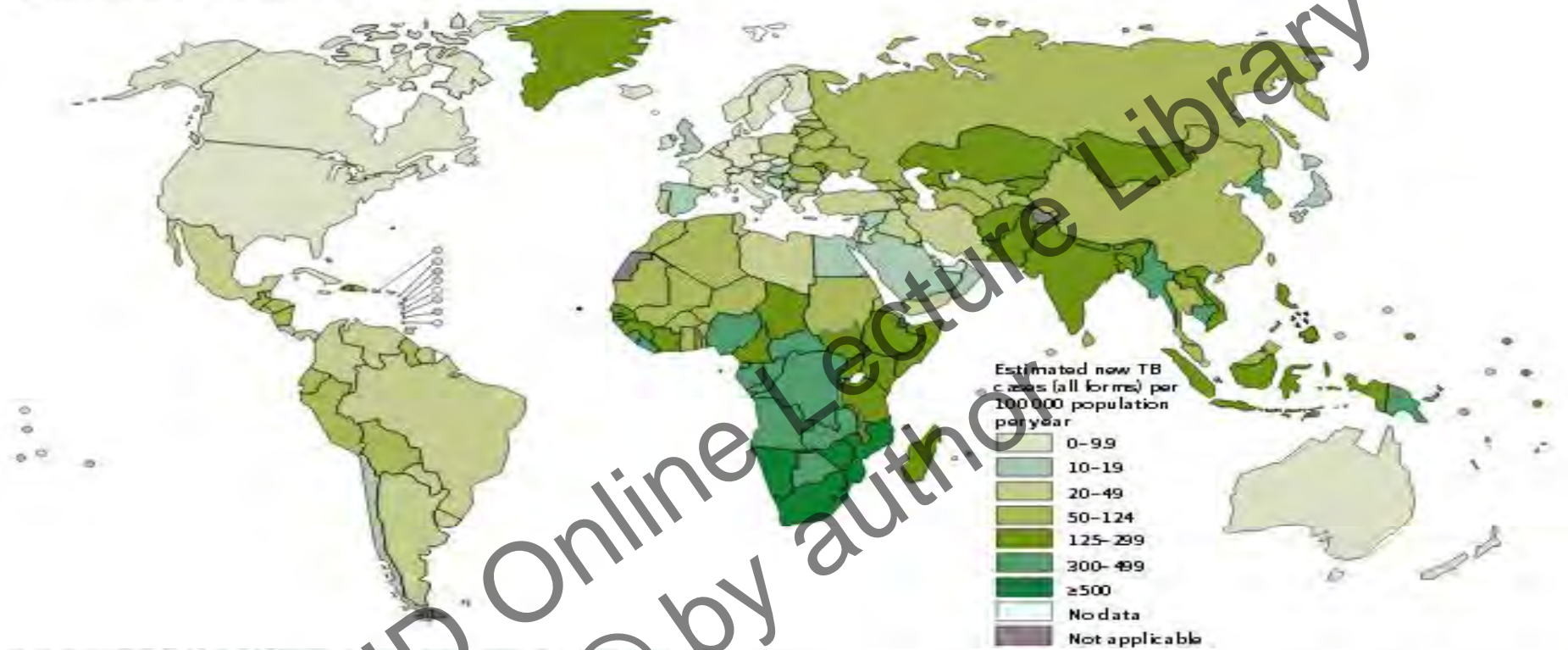
# Incidence of tuberculosis (2013-14)



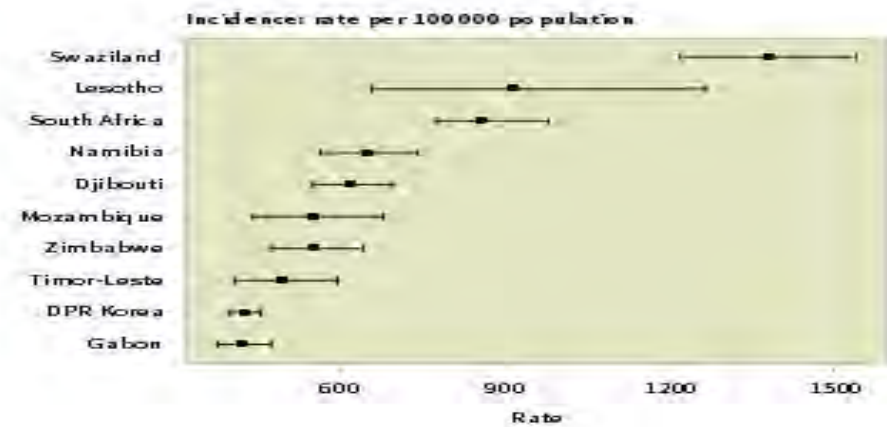
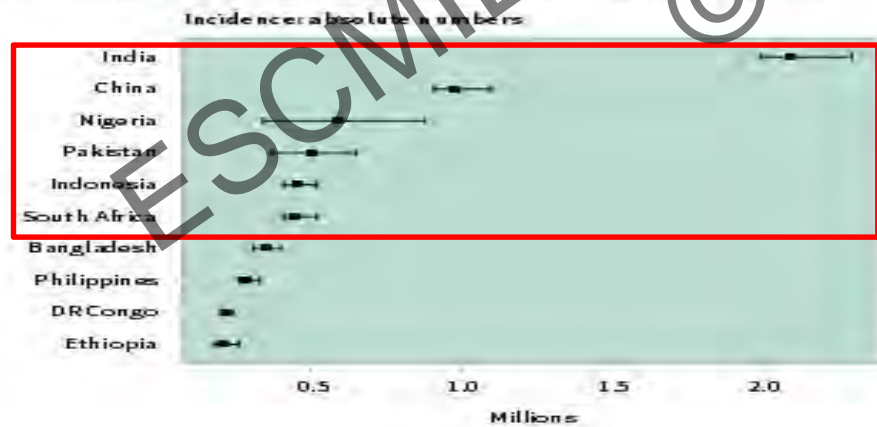
()Percentage of notified cases with bacteriologically confirmed pulmonary tuberculosis  
World Health Organization. Global Tuberculosis Report 2014.



### Estimated TB incidence rates, 2013



### Estimated TB incidence: top ten countries, 2013



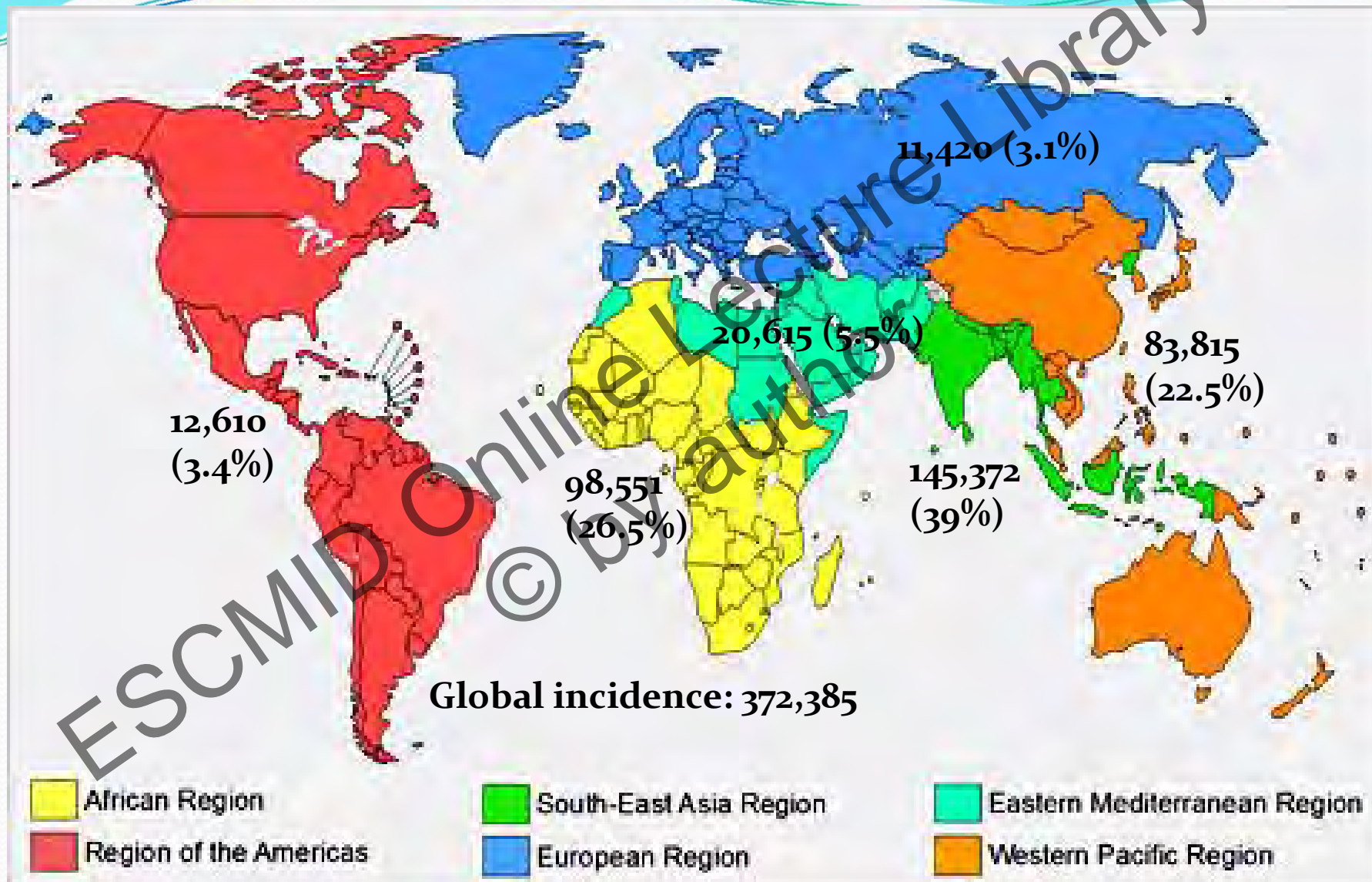
World Health Organization. Global Tuberculosis Report 2014.

## • Demographics of CPA

- Prevalence: 1,173,881 (852,048-1,372,457);
  - 18 per 100,000 population
- Incidence: 372,385
- Maximum burden: South-East Asia and African Regions (65%)
  - India: 290,147
  - Nigeria: 60,383
- Variable global prevalence
  - Cause specific?



# Estimated incidence of CPA



# Prevalence of CPA in pulmonary tuberculosis

Table 3. Relative frequency of pulmonary tuberculosis (PTB) and chronic pulmonary aspergillosis (CPA) for countries with populations exceeding 50 million, 2005

Country	Population <sup>a</sup> (2005)	Annual PTB cases alive at 1 year	Estimated annual CPA cases after PTB	5-year estimated CPA prevalence <sup>b</sup>	5-year estimated CPA prevalence rate <sup>c</sup>
Global total	6 512 276 000	5 899 619	372 385	1 173 881	18.0
China	1 312 253 000	1 052 925	67 387	212 427	16.2
India	1 130 618 000	1 297 047	83 011	261 679	23.1
United States	302 741 000	8 907	588	1 853	0.6
Indonesia	219 210 000	4 208 53	26 935	84 907	38.7
Brazil	186 075 000	70 789	5 663	17 852	9.6
Pakistan	165 816 000	2 049 55	13 117	41 350	24.9
Bangladesh	153 122 000	2 433 61	15 575	49 098	32.1
Russian Federation	148 470 000	1 116 234	7 439	23 450	16.3
Nigeria	140 879 000	3 992 97	19 155	60 383	42.9
Japan	127 449 000	17 724	1 134	3 576	2.8
Mexico	105 330 000	15 326	981	3 092	2.9
Philippines	85 496 000	2 162 28	13 839	43 624	51.0
Viet Nam	84 074 000	97 497	3 412	10 757	12.8
Germany	82 409 000	3 339	100	316	0.4
Egypt	77 154 000	9 266	593	1 869	2.4
Ethiopia	74 661 000	1 247 10	7 981	25 160	33.7
Turkey	71 169 000	11 042	707	2 228	3.1
Islamic Republic of Iran	70 765 000	9 278	594	1 872	2.6
Thailand	65 946 000	64 566	4 132	13 026	19.8
France	61 013 000	5 517	166	522	0.9
United Kingdom	60 261 000	4 189	118	370	0.6
Democratic Republic of the Congo	59 077 000	1 255 38	8 034	25 327	42.9
Italy	58 645 000	2 807	84	265	0.5

<sup>a</sup> From the Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat<sup>28</sup>.

<sup>b</sup> Range provided in Fig. 2.

<sup>c</sup> Per 100 000 population.



# What role does TB play in pulmonary mycoses?

- An open invitation!
- Fungi expected to **infect** 46% cases of pulmonary tuberculosis
- Commonest fungi
  - *Cryptococcus neoformans* (91%)
  - *Histoplasma capsulatum* (82%)
  - *Aspergillus fumigatus* (80%)
  - *A. niger* (28%)

# Why is TB so important to *Aspergillus*?

- Residual cavities in 21-35% treated cases
  - Upto 36% on the CT
- 11-17% tubercular cavities infected by *Aspergillus*
  - Underlying cause in 60-90% cases with aspergilloma
- Cavities  $\geq 2.5$ cm after treatment
  - 1 year later: 36% sensitized to *Aspergillus* spp.
  - 3 years later: 22% radiological aspergillomas
- Underlying cause in 50-70% cases of CPA
- Estimates: 8-12% treated cases of classical pulmonary TB develop CPA



# Is it always *Mycobacterium tuberculosis*?

- No!
- Sporadic reports of NTM
  - *Mycobacterium avium* (Kobashi Y et al. Intern Med 2005;44: 246-50.)
  - *M. xenopi* (Andre'jak C et al. Thorax 2009; 64: 291-296.)
  - *M. kansasii* (Maliwan N et al. Postgrad Med J 2005; 81: 530-3.)
  - *M. malmoeense* (Gomez-Abreo D, et al. Rev Mal Respir. 2012;29:435-9.)
- Reasons for association unknown
  - Give and take relationship?

# How does CPA present?

- CPA presents like **tuberculosis**.
  - Chronic indolent course
  - Non-specific symptoms
    - Weight loss
    - Cough
    - Shortness of breath
    - Hemoptysis
    - Fatigue and malaise
    - Chest pain
    - Sputum production
    - Fever



- **Radiological**

- Ill-defined infiltrates
  - Bilateral upper lobe
- Single/multiple cavities
- Expanding cavities
- Pericavitary infiltrates
- Pleural thickening
- Fungal ball



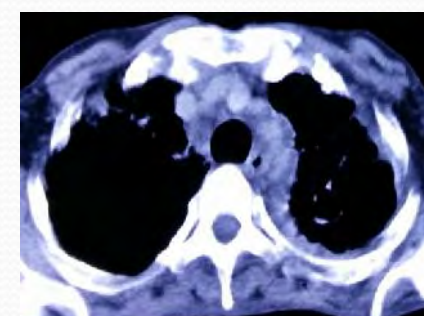
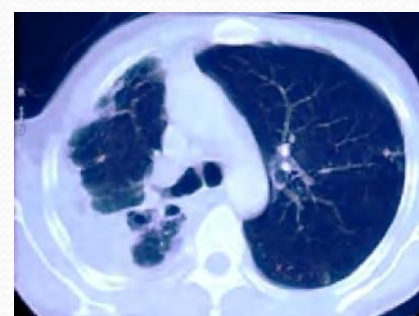
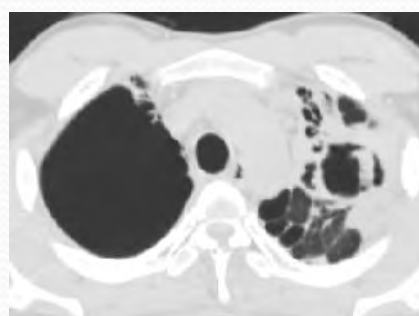
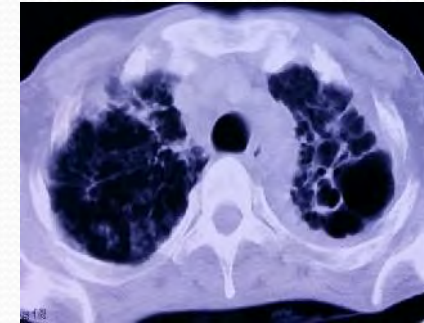
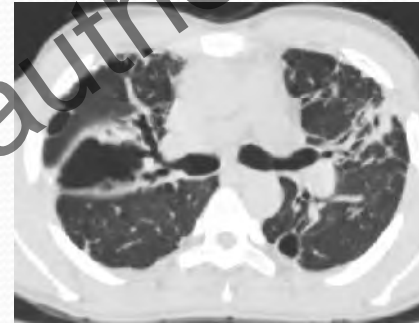
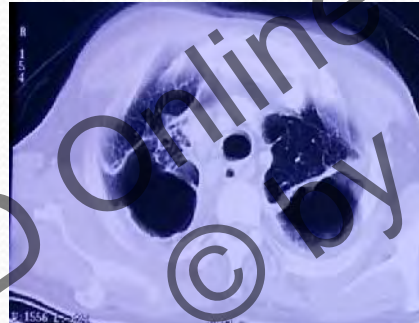
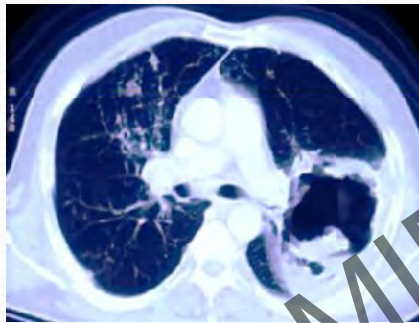
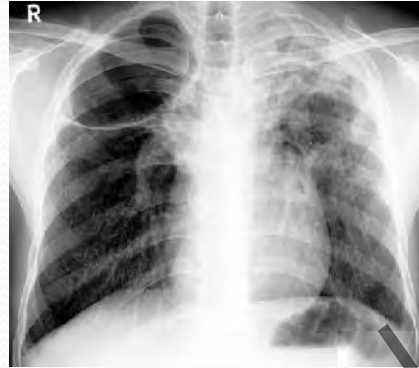
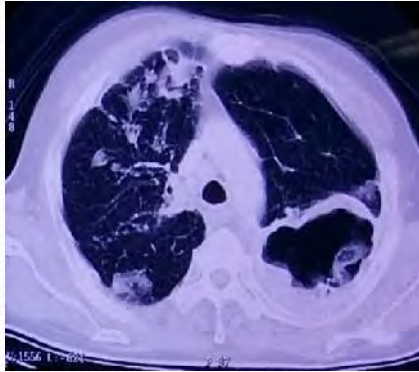
Comparison with previous radiographs usually essential

# What are the radiological patterns in CPA?

- Chronic cavitating pulmonary aspergillosis (CCPA)
- Chronic fibrosing pulmonary aspergillosis (CFPA)
- Chronic necrotizing pulmonary aspergillosis (CNPA)/Sub-acute invasive aspergillosis



# Radiological patterns in CPA



CNPA

CCPA

CFPA

????

## How is CPA diagnosed?

- Clinico-radio-micro-serological diagnosis
  - Sputum/BAL
- **Exclusion of other obvious causes**
  - Tuberculosis
- Presence of hyphae not essential



# Diagnostic criteria for CPA

- All of the following:
  - Chronic (duration of >3 months) pulmonary or systemic symptoms
  - Exclusion of other likely pulmonary pathogens
  - No major discernible immunocompromising factors (except for patients with CNPA)
  - Radiological evidence of a progressive (over months or years) pulmonary lesion with surrounding inflammation, with or without an intracavitary mass
  - Precipitating (IgG) antibody to *Aspergillus* in serum
  - Persistently elevated inflammatory markers (CRP, ESR or plasma viscosity)

# How is CPA treated?

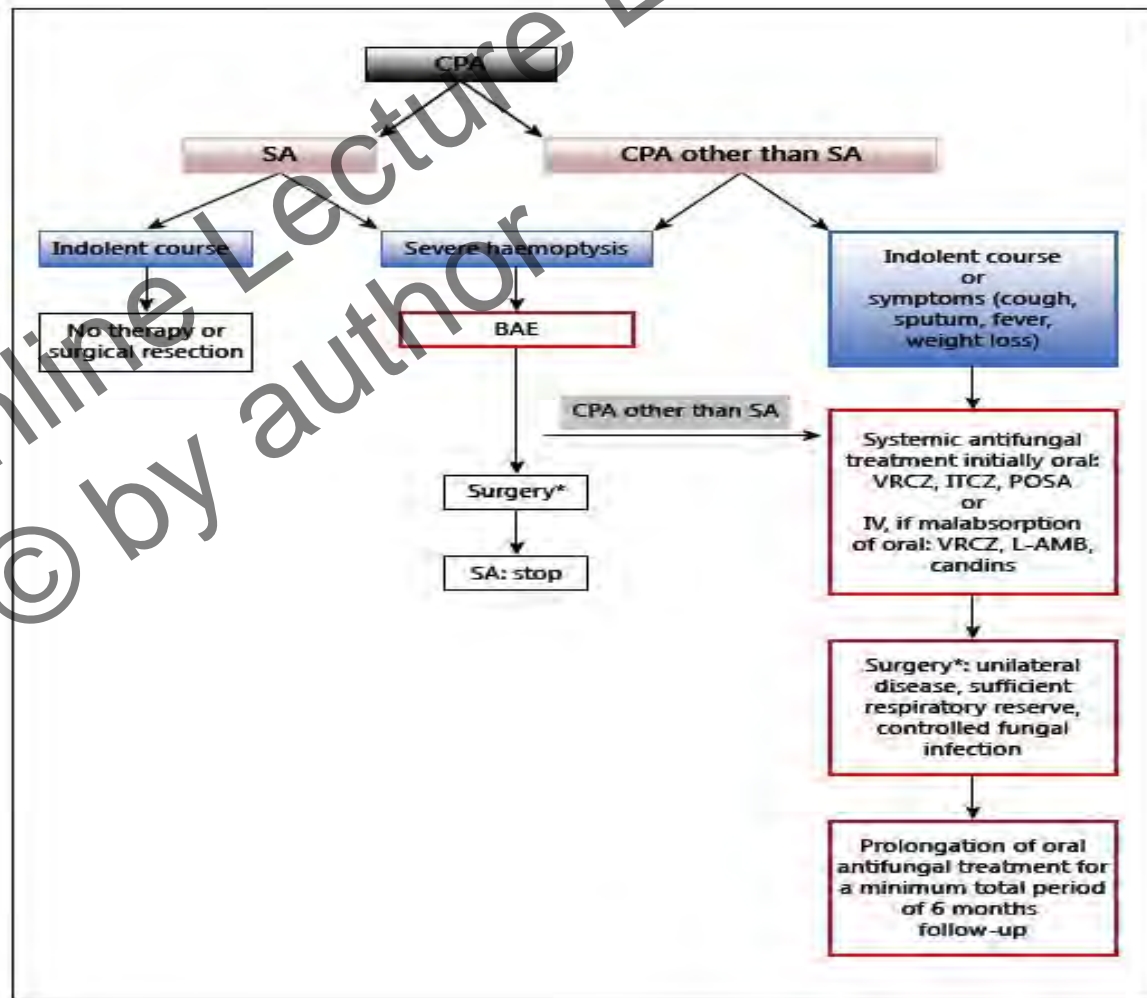
- Control of haemoptysis
- Antifungals
  - **Itraconazole**
  - Voriconazole
  - Posaconazole
  - AMB (L)
  - Echinocandins
- Surgical resection
  - Lobectomy, pneumonectomy, atypical resection, cavernostomy, thoracoplasty

Poor response

Triazole  
antifungal  
resistance



# Treatment strategy for CPA



**Fig. 4.** Proposal for a global therapeutic strategy algorithm of CPA. ITCZ = Itraconazole; L-AMB = liposomal amphotericin B; POSA = posaconazole; SA = simple aspergilloma; VRCZ = voriconazole.

# What is the prognosis in CPA?

## Bad prognostic indicators

- Advanced age
- Systemic comorbidities
- Baseline corticosteroid use
- BMI <18.5 Kg/m<sup>2</sup>
- CRP of ≥5.0 mg/dL

Nakamoto K et al. Intern Med 2013; 52: 727-734.

## Antifungals and survival

- No improvement  
(Ohba H et al. Respir Med 2012;106: 724-9)
- Itraconazole
  - 76% reponse  
(Agarwal R et al. Mycoses 2013; 56: 559-70.)
- Voriconazole
  - ≥50% improvement  
(Cadranel J et al. Eur J Clin Microbiol Infect Dis 2012; 31: 3232-9.)
- Posaconazole
  - 61% reponse at 6 months, 46% at 1 year  
(Felton TW et al. Clin Infect Dis 2010; 51: 1383-91.)
- Micafungin
  - As good as Voriconazole  
(Kohno S et al. J Infect 2010;61:410-8.)



# Recurrence of CPA after stopping treatment

- 36% recurrence noted within 1 year
  - Itraconazole and Voriconazole
  - Median treatment duration-778 days
- Reappearance of antibodies good marker of relapse
- “Adequate treatment” needs to be defined

# What are the implications of misdiagnosis?

- Mortality attributable to CPA: 10-30 %
- Recurrent hospital visits for persistent symptoms
  - Signed off as intractable hemoptysis due to aspergilloma and/or infections
  - Progressive loss of lung function
- Sputum-negative tuberculosis
  - Misdiagnosed and mistreated
  - Inflated burden
- Empirical therapy
  - Drug interactions between azoles and ATT/ART



# CPA in patients with tuberculosis: The Indian perspective

**Table 2.** Pulmonary tuberculosis (TB) estimates in the Indian population.


Total population in 2011	1,210,569,573
Incident TB cases	2,130,602
Annual pulmonary TB case alive at 1 year	1,438,157
Estimated annual CPA cases after Pulmonary TB	92,042
5-year estimated CPA prevalence	290,147
5-year estimated CPA prevalence rate (per 100,000)	24

CPA: chronic pulmonary aspergillosis.

- Aspergilloma
  - 79.6% associated with tuberculosis
- Antibodies against *Aspergillus* spp.
  - 26-27 % patients with tuberculosis
  - 23% patients with chronic lung disease

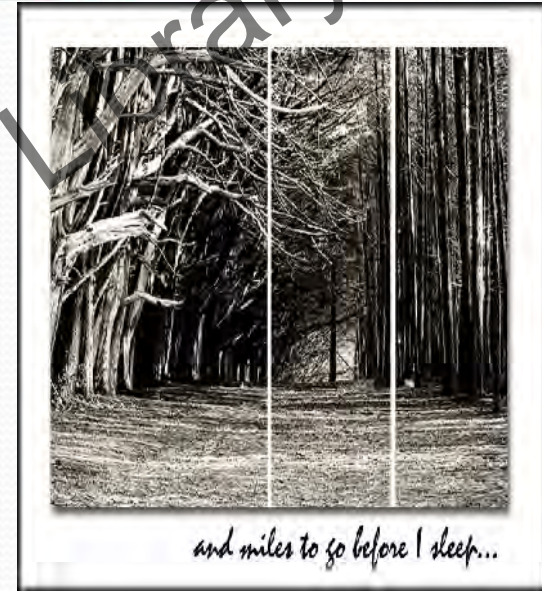
Shah R, et al. Indian J Pathol Microbiol 2008;51:342-5  
Shahid M et al. Indian J Med Microbiol 2001; 19:201-205.  
Dhooria S et al. Int J Tuberc Lung Dis 2014;18:85-855.  
Kurhade AM et al. Indian J Med Microbiol 2002;20: 141-144.



- 
- Likely to be underestimated
    - Poor recognition
    - Those treated outside the National programme
    - Other cavitating disorders not explored
    - No definite numbers
  - Expected to increase with better outcomes of tuberculosis
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# Future directions

- Understand the pathogenesis
- Greater awareness among clinicians
- Ascertain the true population prevalence
- Determine cause-specific attributable rates for risk factors
- Update treatment parallel to antifungal susceptibility data





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