



# Sporotrichosis

Yu Zhang & Ruoyu Li MD



# Disclosure

- There is no conflict of interest to declare.

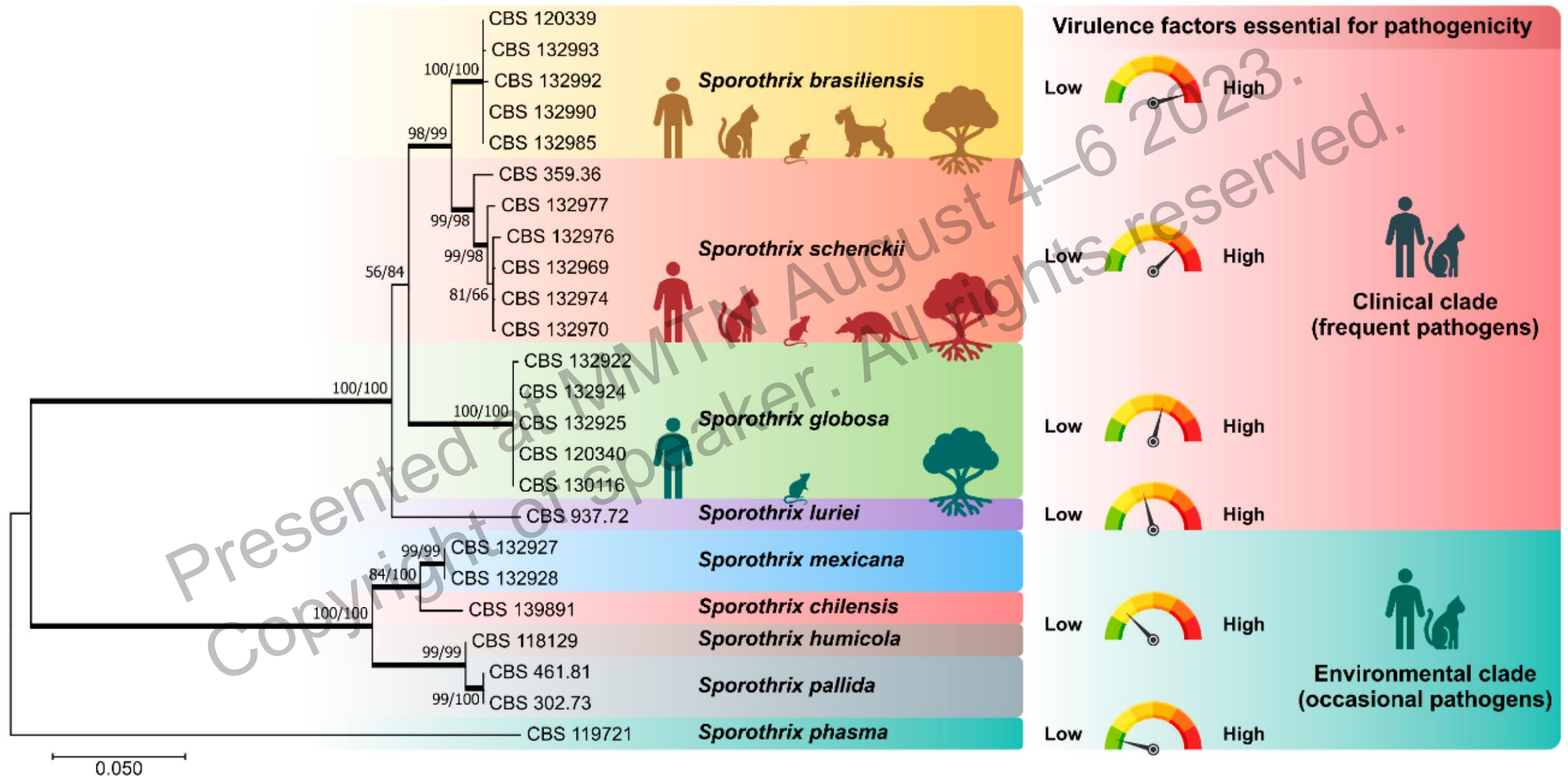
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# History

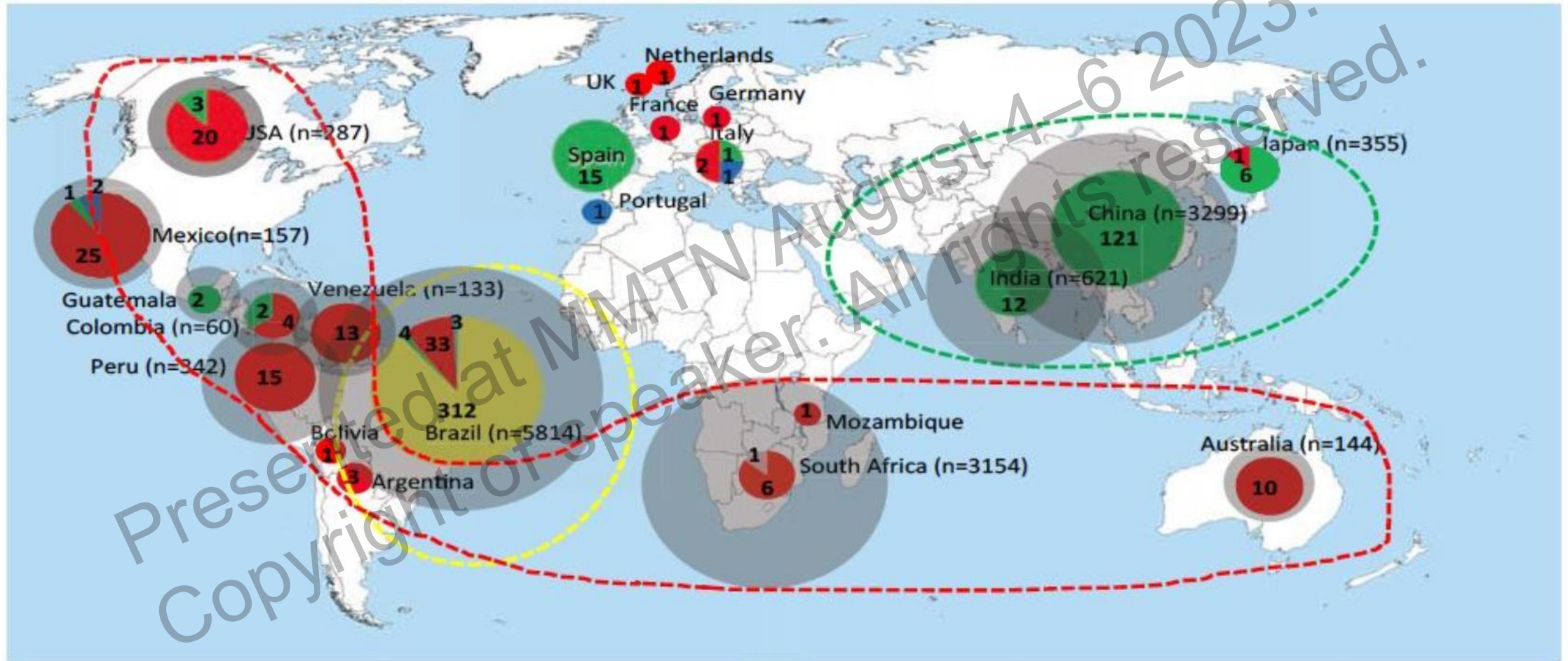


- In 1896, *Sporothrix schenckii* was first isolated by Benjamin Schenck
- In 1907, first zoonotic human case from rat in Brazil
- In 1960, Howard confirmed its **dimorphic nature**

# *Sporothrix* comprises approximately 53 species



# epidemiology



● Sb   
 ● Ss   
 ● Sg   
 ● Sm   
 ● Sl

# Outbreak in China

## China

- > 3000 documented cases
- High endemicity are **northeastern China**
- Farmer or people live in rural areas, M/F ratio: 1/1.5
- Source: **reeds, cornstalks, soil**
- No animal cases yet



# Outbreak in Australia

## Australia



- 16 cases over 9 months
- Source: **mouldy hay**



- 31 cases, rainfall season
- Exposure – injuries in the **garden, bushland**

- **Hay supplier & cases related hay samples were positive for *S. schenckii***

Sivagnanam S, et al. *Med J Aust* 2012; 196: 588  
Conias & Wilson. *Australasian J Dermatol* 1998; 39: 34-7  
Fenney KT, et al. *Emerg Infect Dis* 2007; 13: 1228-31

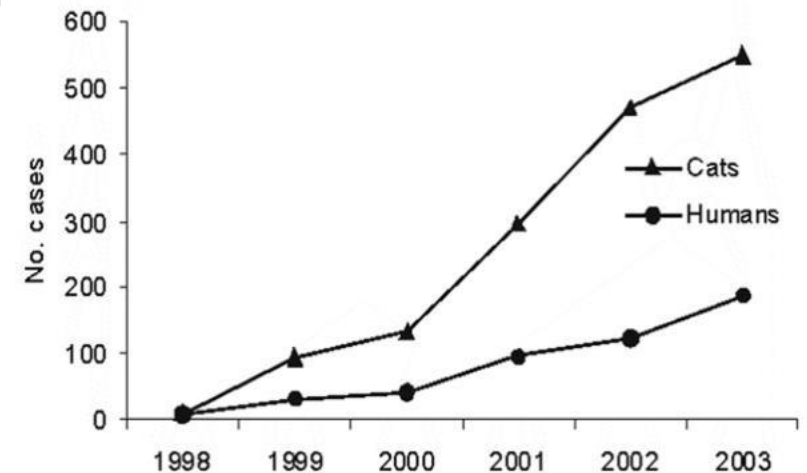


# Outbreak in Brazil

## ■ Brazil



- Human cases 759, dogs 64, cats 1503
- 85% dogs & 83% patients reported contact with **cats**
- 56% humans reported cat bites or scratches
- Sporotrichosis in cats preceded occurrence among owners



Schubach A. Emerg Infect Dis 2005; 11: 1952

Schubach A et al. Curr Opin Infect Dis 2008; 21: 129

Rodrigues AM. PLOS Neg Trop Dis 2013; 7: e2281



# Transmission



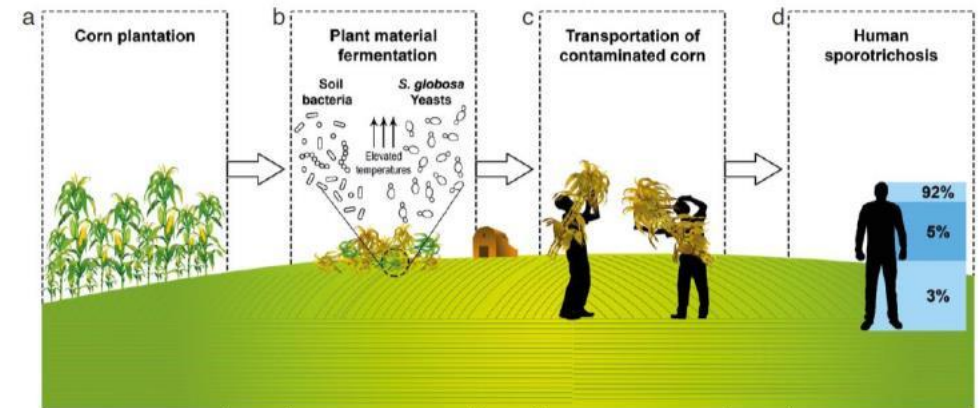
## ? Plant materials

- rose, hay, reed, cornstalk, wood

## ? Animal

- cat, dog, armadillos, horse, rat, fish, insect, etc.

## ? Soil



# Transmission

- Unusual complication associated with **fire ant** stings.
- Painful and pruritic pustules that resolve later, secondary bacterial infections and anaphylactoid reactions.
- Speculation: organism was present on the patient's skin and was introduced by the sting, alternatively, present on the ant's stinger itself.



# Transmission

- **Age: 3 – 10 mo**
- **M/F ratio: 2/1**
- **Types: 73.3% (11/15) FC**
- **Location: Jilin Province**
- **No history of trauma, nor contact of animal**
- **Cornstalks may be the source of infections**

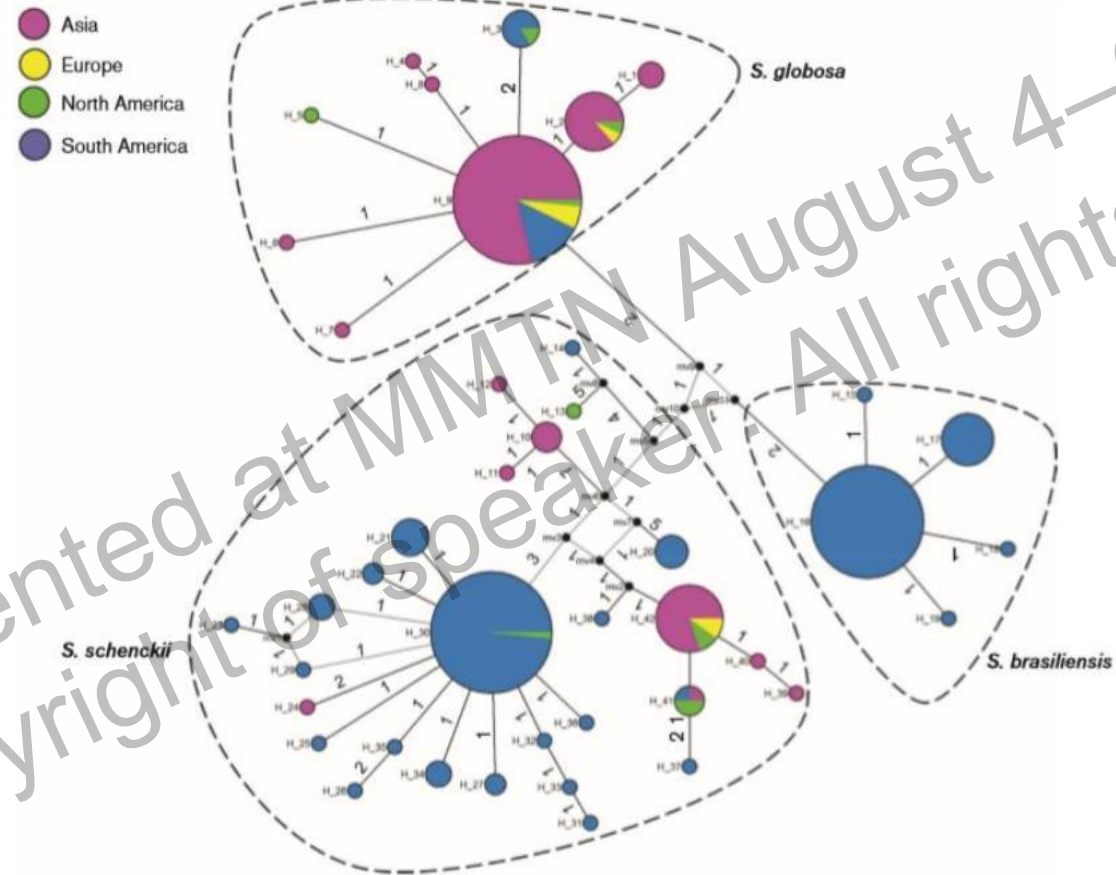


# Updated epidemiology in Asia



Feng P, et al. Origin and distribution of *Sporothrix globosa* causing sporotrichosis in Asia. *J Med Microbiol.* 2017 May;66(5):560-569.

# Update epidemiology of sporotrichosis in Asia



**Fig. 4.** Haplotype network of *CAL* sequences of 281 *Sporothrix* isolates. Haplotypes are represented by pie charts with the circumference proportional to the haplotype frequency. The small black dots [median vectors (mv)] represent internal haplotypes not present in the dataset. Numbers on the lines indicate mutation steps between the haplotypes.

Feng P, et al. Origin and distribution of *Sporothrix globosa* causing sporotrichosis in Asia. *J Med Microbiol.* 2017 May;66(5):560-569.

# Clinical manifestation

## **Cutaneous forms (common)**

- **Fixed cutaneous**
- **Lymphocutaneous**
- **Disseminated cutaneous**

## **Extracutaneous forms (rare)**

- **Pulmonary**
- **Osteoarticular**
- **Meningitis**
- **Disseminated**

# Clinical manifestation

## Fixed cutaneous form



# Clinical manifestation

## □ Lymphocutaneous form



Handattu Sripathi, International Journal of Dermatology 2009, 48, 1198–1200

Elsa Vásquez-del-Mercado, et al. Clinics in Dermatology (2012) 30, 437–443



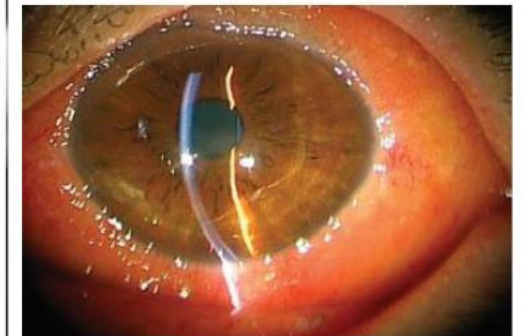
# Clinical manifestation

## Disseminated cutaneous



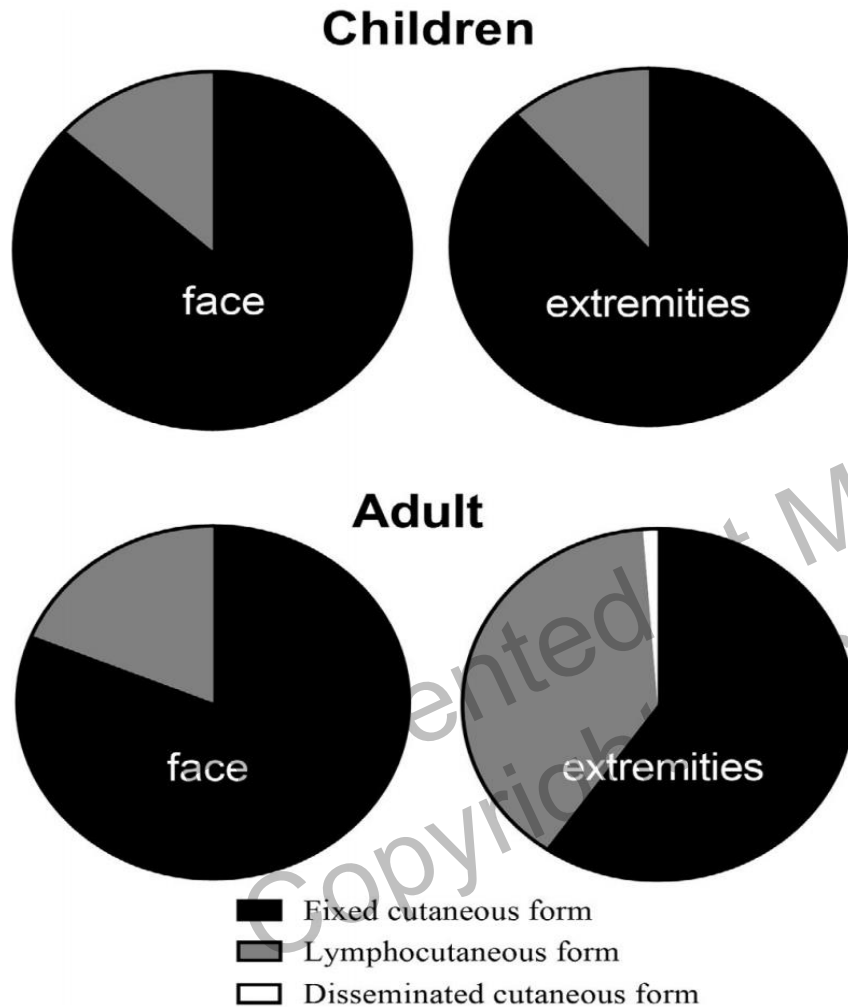
mainly in alcoholics, diabetes, HIV, etc. patients

## Extracutaneous forms



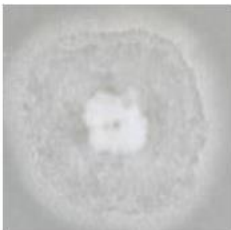
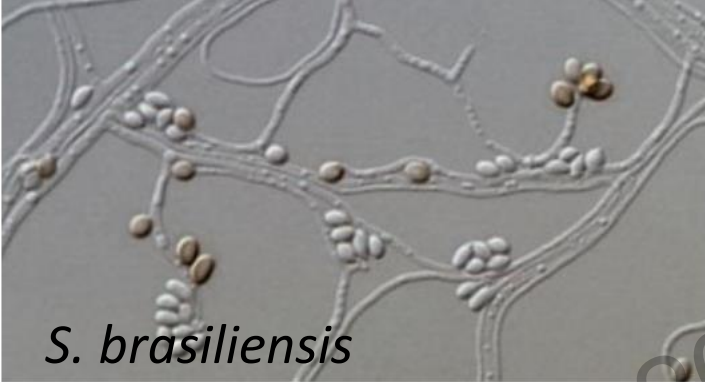
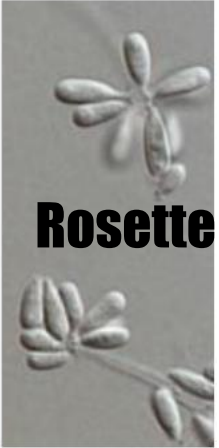
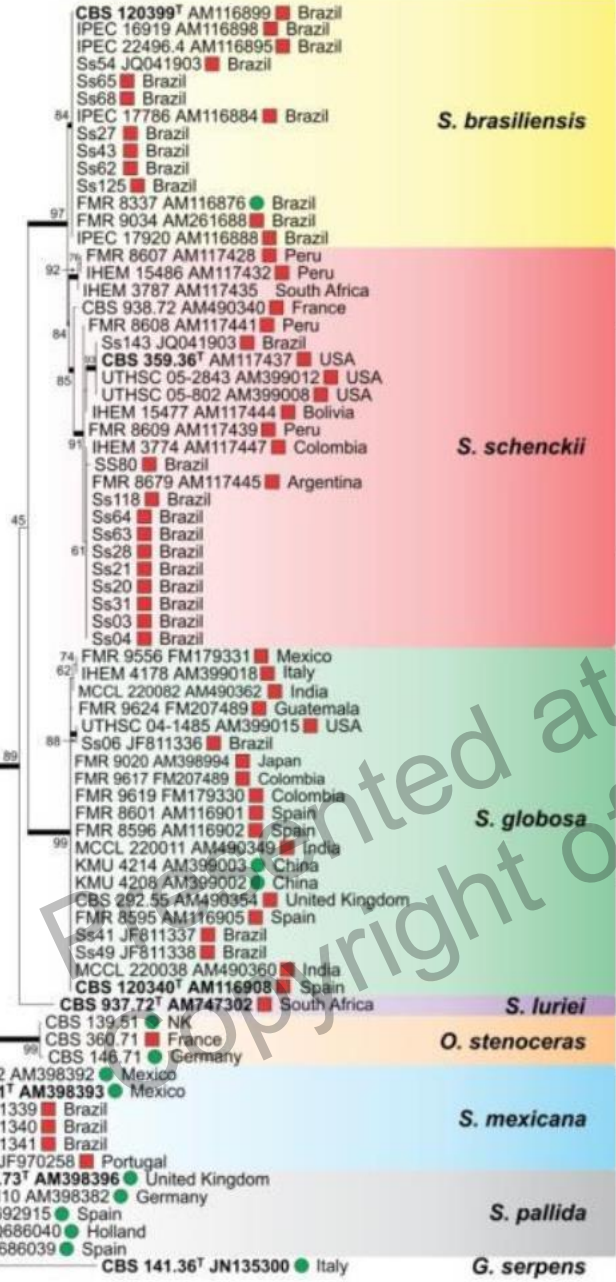
Appenzeller S, et al. Clin Rheumatol 2006; 25: 926;  
Wang JP, et al. Clin Infect Dis 2000; 31: 615  
Kashima T et al. Cornea 2010; 29: 573-6

# The location and type of lesions in adults and children are different



# Morphology & phylogeny

■ Clinical  
● Environmental



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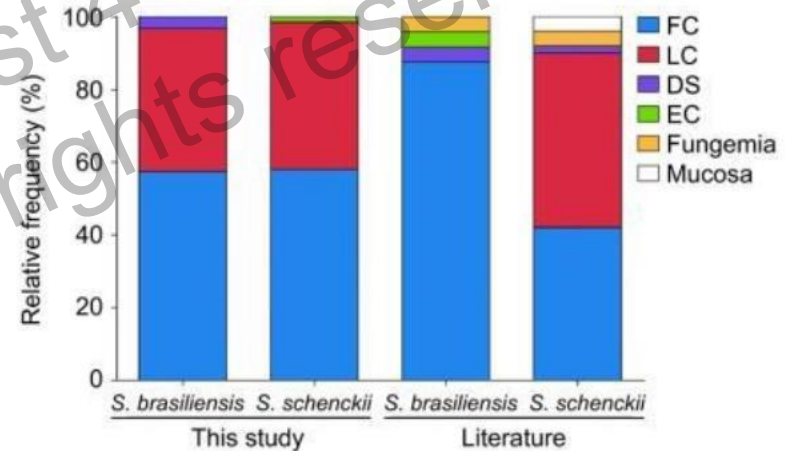
# Difference features of *Sporothrix* sp.

## Transmission



Barros MB de L et al, Clin Microbiol Rev 2011

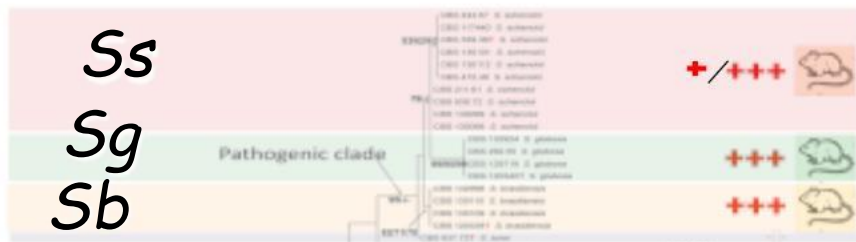
## Clinical features



More atypical manifestation in *S. brasiliensis*

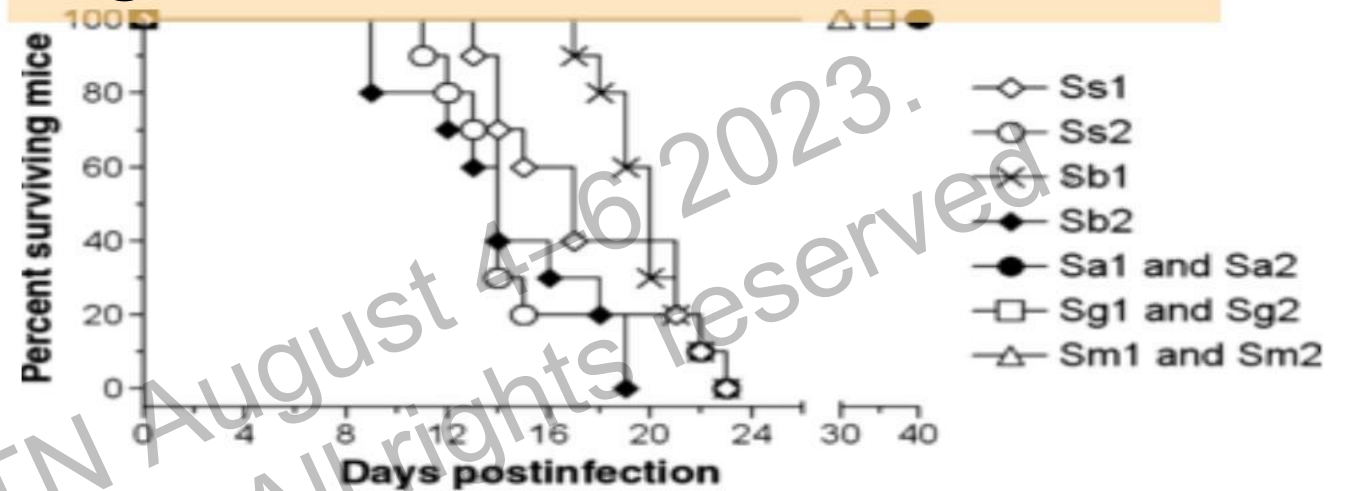
Rodrigues AM, et al. Emerging Microbes & Infections 2014

# Virulence



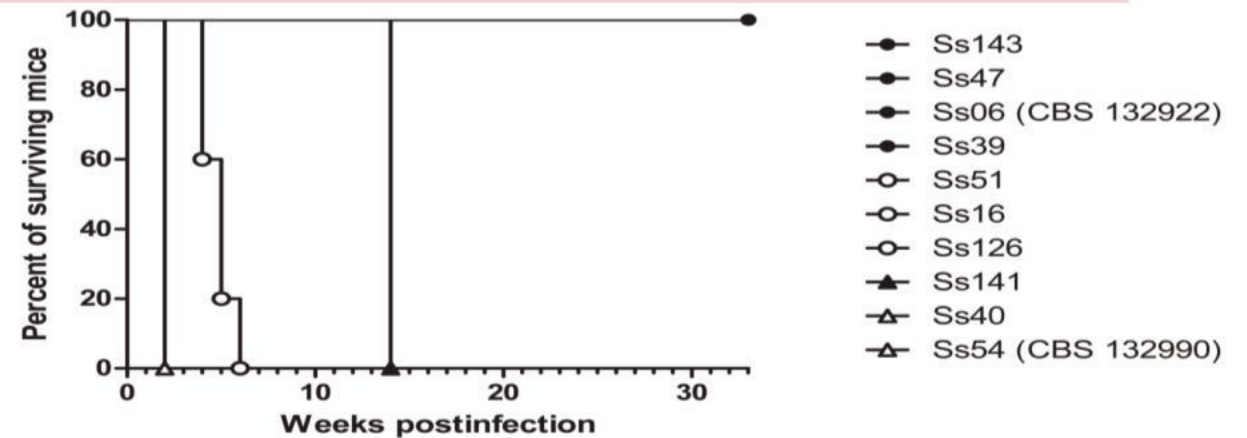
Lowest virulence in *S. globosa*

Highest virulence in *S. brasiliensis*



Arrillaga-Moncrieff et al. Clin Microbiol Infect. . 2009

Different virulence in *S. schenckii*

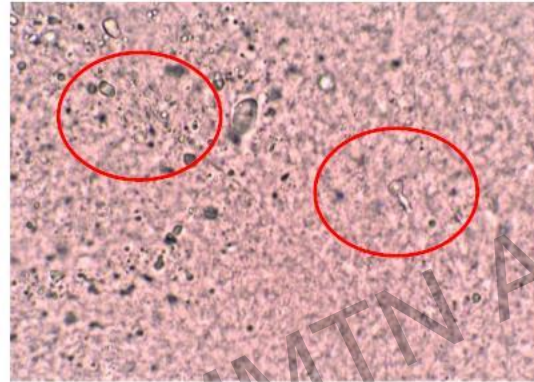


Yu et al. Personia. 2015

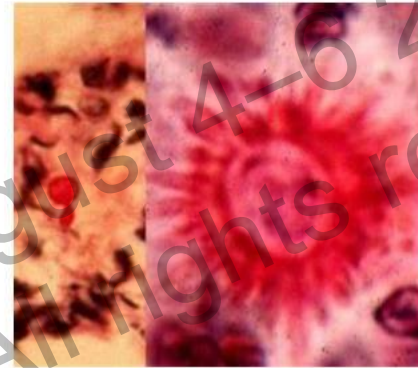
Fernandes et al. Virulence. 2013

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# Laboratory examination



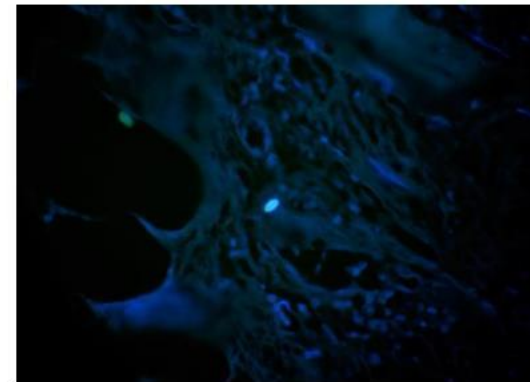
**10% KOH**



**Histopathology**

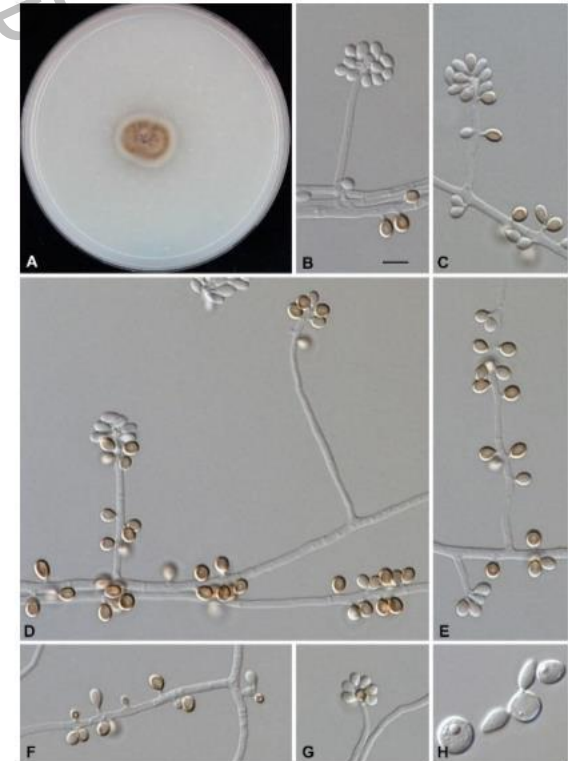


**Smear**



**Biopsy tissue**

**Fungal florescent stain**



**Fungal culture**

# Molecular diagnostic methods



## Review Article

### Sporotrichosis between 1898 and 2017: The evolution of knowledge on a changeable disease and on emerging etiological agents.

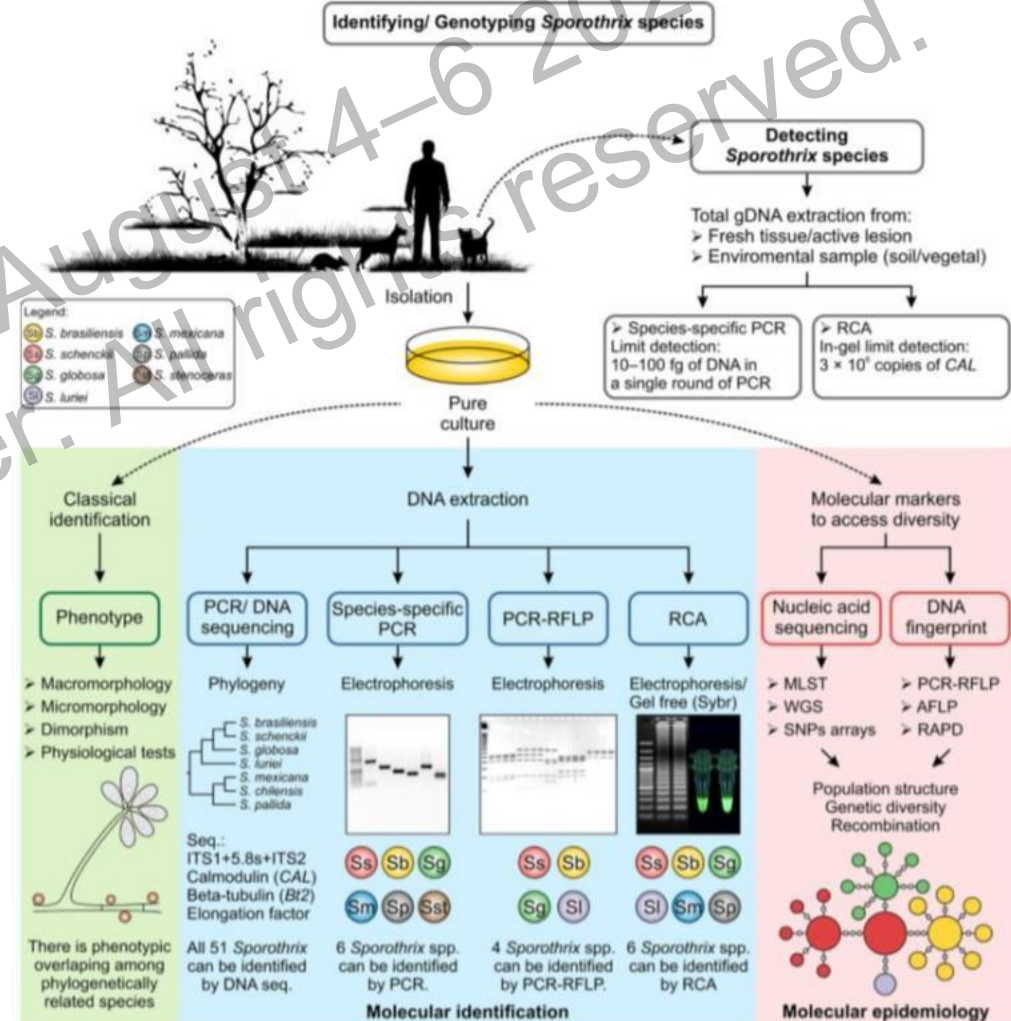
Leila M. Lopes-Bezerra<sup>1,\*</sup>, Hector M. Mora-Montes<sup>2,#</sup>, Yu Zhang<sup>3</sup>,  
Gustavo Nino-Vega<sup>2</sup>, Anderson Messias Rodrigues<sup>4</sup>,  
Zoilo Pires de Camargo<sup>4</sup> and Sybren de Hoog<sup>5</sup>

#### RESEARCH ARTICLE

### Molecular Diagnosis of Pathogenic *Sporothrix* Species

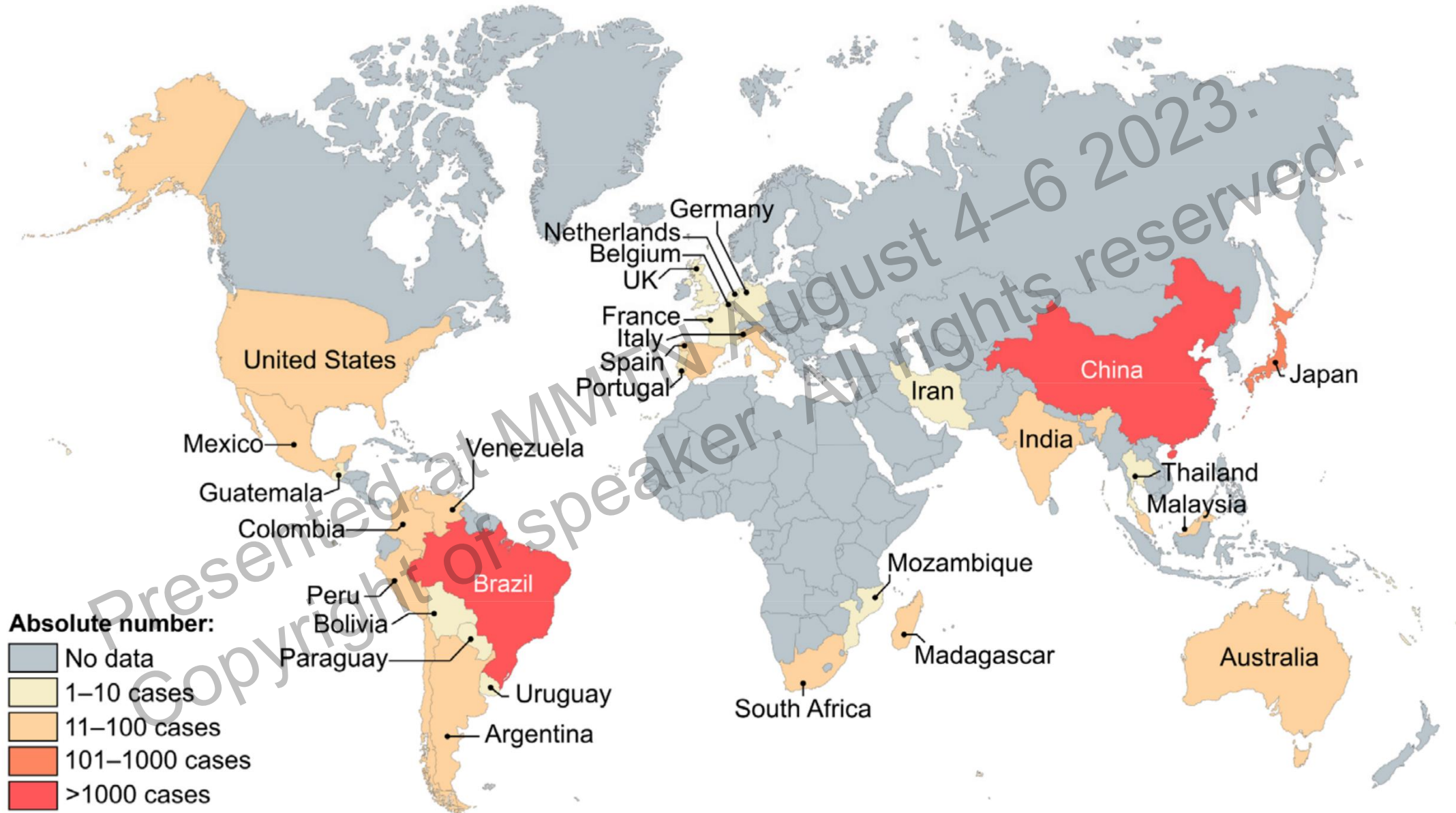
Anderson Messias Rodrigues<sup>1\*</sup>, G. Sybren de Hoog<sup>2</sup>, Zoilo Pires de Camargo<sup>1\*</sup>

<sup>1</sup> Departamento de Microbiologia, Imunologia e Parasitologia, Disciplina de Biologia Celular, Universidade Federal de São Paulo (UNIFESP), São Paulo, São Paulo, Brazil, <sup>2</sup> CBS-KNAW Fungal Biodiversity Centre, Utrecht, The Netherlands



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## Molecular diagnosis of sporotrichosis





# Molecular diagnostic methods



Medical Mycology, 2019, 0, 1–5  
doi: 10.1093/mmy/myz029  
Advance Access Publication Date: 0 2019  
Original Article



## Original Article

### Development and evaluation of a real-time polymerase chain reaction for fast diagnosis of sporotrichosis caused by *Sporothrix globosa*

Mingrui Zhang<sup>1</sup>, Fuqiu Li<sup>1,\*</sup>, Jie Gong<sup>2</sup>, Xin Yang<sup>3</sup>, Jianzhong Zhang<sup>2</sup> and Fei Zhao<sup>2,\*</sup>



#### RESEARCH ARTICLE

### Fast diagnosis of sporotrichosis caused by *Sporothrix globosa*, *Sporothrix schenckii*, and *Sporothrix brasiliensis* based on multiplex real-time PCR

Mingrui Zhang<sup>1</sup>, Fuqiu Li<sup>1,\*</sup>, Ruoyu Li<sup>2,3</sup>, Jie Gong<sup>2</sup>, Fei Zhao<sup>2,\*</sup>

<sup>1</sup> Department of Dermatology, the Second Hospital of Jilin University, Changchun, Jilin Province, China, <sup>2</sup> Department of Dermatology, Peking University First Hospital, Beijing, China, <sup>3</sup> Beijing Key Laboratory of Molecular Diagnosis on Dermatoses, Beijing, China, <sup>4</sup> National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, State Key Laboratory of Infectious Disease Prevention and Control, Beijing, China

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OPEN

Emerging Infectious Diseases (2017) 6, e68. doi:10.1093/eid/17.7.5

## ORIGINAL ARTICLE

### Genetic variation of *Sporothrix globosa* isolates from diverse geographic and clinical origins in China

Lipei Zhao, Yan Cui, Yu Zhen, Lei Yao, Ying Shi, Yang Song, Ruili Chen and Shanshan Li

Table 2 Morphological characteristics and AFLP genotypes of *Sporothrix globosa* isolates in China

Group by AFLP	Number of isolates	Mean colony diameter (mm) ± SD			Growth rate (mm/week) ± SD		
		30 °C	35 °C	37 °C	30 °C	35 °C	37 °C
I	52	29.89 ± 5.02 <sup>a</sup>	6.48 ± 2.16 <sup>a</sup>	3.12 ± 1.17 <sup>a</sup>	9.96 ± 1.67 <sup>a</sup>	2.16 ± 0.27 <sup>a</sup>	1.04 ± 0.39 <sup>a</sup>
II	93	31.86 ± 5.02 <sup>a</sup>	8.58 ± 2.20 <sup>b</sup>	2.54 ± 0.63 <sup>b</sup>	10.62 ± 1.67 <sup>a</sup>	2.86 ± 0.73 <sup>b</sup>	0.85 ± 0.21 <sup>b</sup>
III	2	32.00 ± 2.83 <sup>a,b</sup>	9.50 ± 0.71 <sup>a,b</sup>	4.95 ± 0.07 <sup>c</sup>	10.67 ± 0.94 <sup>a,b</sup>	3.17 ± 0.24 <sup>a,b</sup>	1.65 ± 0.02 <sup>c</sup>
IV	49	34.53 ± 3.25 <sup>b</sup>	9.21 ± 2.34 <sup>b</sup>	2.56 ± 0.72 <sup>a,b</sup>	11.51 ± 1.08 <sup>b</sup>	3.07 ± 0.78 <sup>b</sup>	0.85 ± 0.24 <sup>a,b</sup>
V	12	32.73 ± 6.04 <sup>a,b</sup>	9.67 ± 3.22 <sup>b</sup>	3.20 ± 1.15 <sup>a,b</sup>	10.91 ± 2.01 <sup>a,b</sup>	3.22 ± 1.07 <sup>b</sup>	1.07 ± 0.38 <sup>a,b</sup>
VI	2	34.25 ± 1.06 <sup>a,b</sup>	8.25 ± 2.47 <sup>a,b</sup>	2.40 ± 0.28 <sup>a,b,c</sup>	11.42 ± 0.35 <sup>a,b</sup>	2.75 ± 0.82 <sup>a,b</sup>	0.80 ± 0.09 <sup>a,b,c</sup>
VII	3	33.83 ± 5.80 <sup>a,b</sup>	10.3 ± 0.58 <sup>a,b</sup>	3.23 ± 0.84 <sup>a,b,c</sup>	11.28 ± 1.93 <sup>a,b</sup>	3.44 ± 0.19 <sup>a,b</sup>	1.08 ± 0.28 <sup>a,b,c</sup>
VIII	3	25.83 ± 3.75 <sup>a,b</sup>	6.17 ± 0.29 <sup>a,b</sup>	2.97 ± 0.35 <sup>a,b</sup>	8.61 ± 1.25 <sup>a,b</sup>	2.06 ± 0.10 <sup>a,b</sup>	0.99 ± 0.12 <sup>a,b</sup>
total	216	31.9 ± 4.97	8.26 ± 2.49	2.76 ± 0.90	10.67 ± 1.66	2.75 ± 0.83	0.92 ± 0.30

n = 0.05; a, b, c = Groups; Nine isolates were excluded since they were not clustered into the AFLP groups.

表 1 常见孢子丝菌分子分型方法的比较

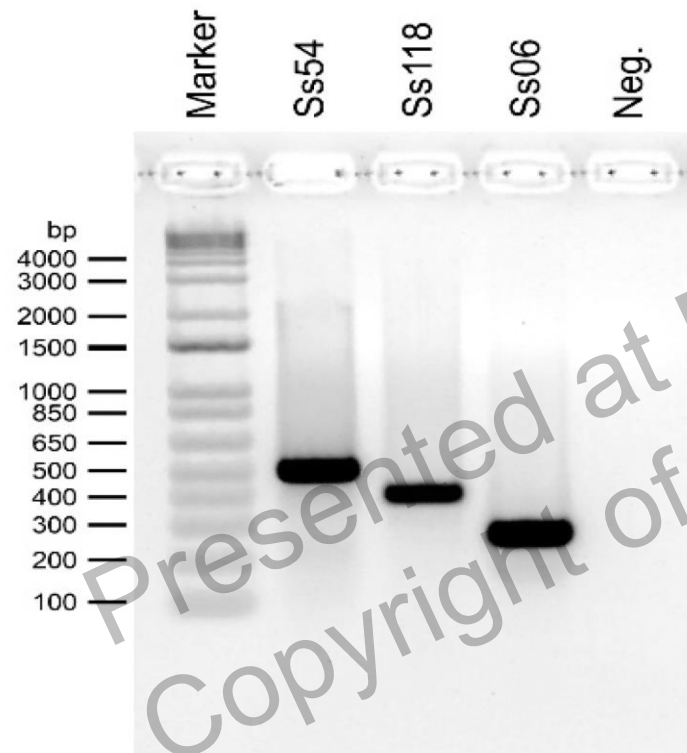
Table 1 Comparison of genotyping studies for *Sporothrix* complex

项目	RFLP	PFGE	RAPD	AFLP	MLST	MLP
Item						
实验技术	酶切+电泳	酶切+电泳	PCR+电泳	酶切+PCR+电泳	PCR+测序	PCR+测序
Techniques	Enzyme digestion+gel electrophoresis	Enzyme digestion+gel electrophoresis	PCR+gel electrophoresis	Enzyme digestion+PCR+gel electrophoresis	PCR+sequencing	PCR+sequencing
分辨力	高	高	中	高	高	高
Discrimination	High	High	Medium	High	High	High
重复性	中	中	差	中	好	好
Repeatability	Medium	Medium	Low	Medium	High	High
可比性	差	差	差	中	好	好
Comparability	Low	Low	Low	Medium	High	High
操作难易	中	难	易	难	易	易
Operation	Medium	Difficult	Easy	Difficult	Easy	Easy
耗时长短	中	长	短	长	中	中
Time-consuming	Medium	Long	Short	Long	Medium	Medium

# Species-specific PCR and qPCR

## A Singleplex species-specific PCR (CAL)

Rodrigues *et al.*

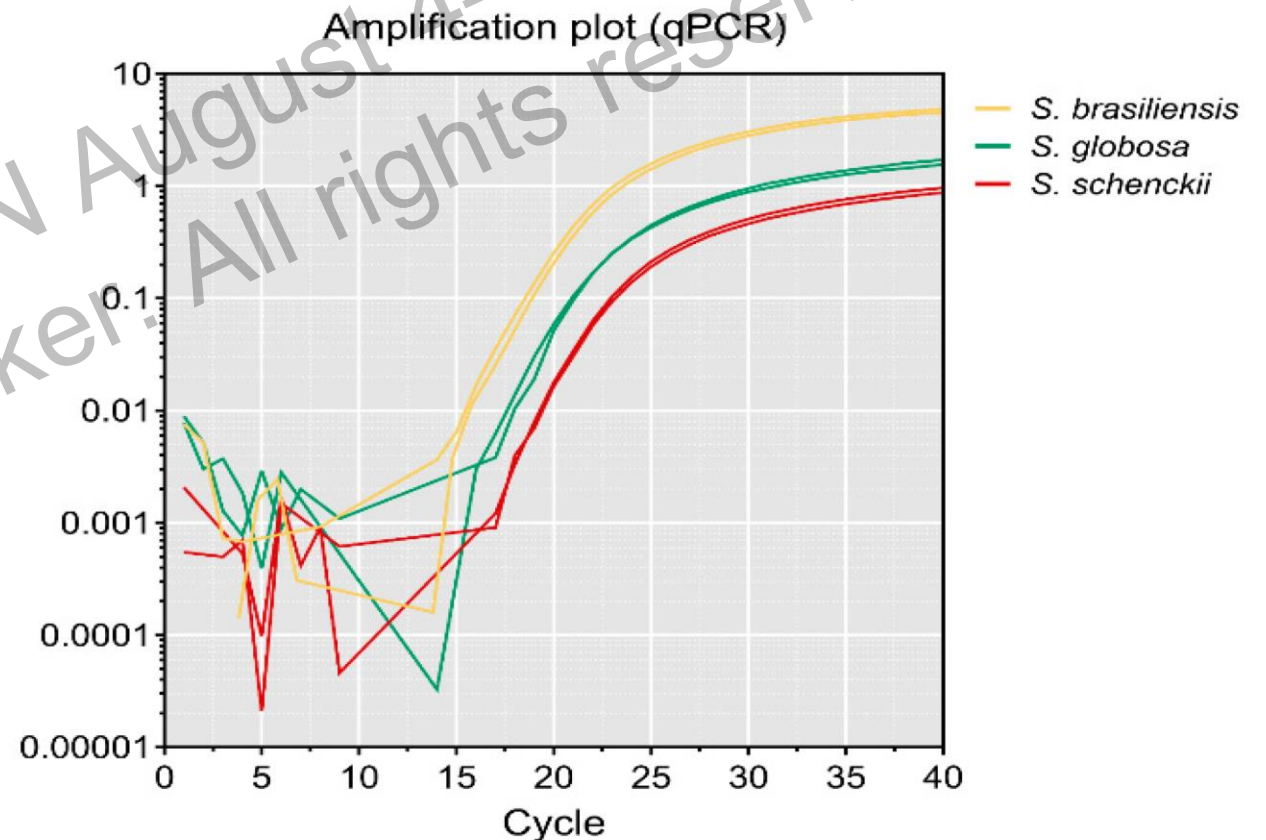


Primers: **Sbra** **Ssch** **Sglo**

Amplicon size (bp): 469 331 243

## B Triplex-probe qPCR assay (BT2)

Della Terra *et al.*



# Molecular diagnostic methods: MALDI-TOF



## Development and optimization of a new MALDI-TOF protocol for identification of the *Sporothrix* species complex

Manoel Marques Evangelista Oliveira<sup>a,b,c,\*</sup>, Cledir Santos<sup>b,d</sup>, Paula Sampaio<sup>c</sup>, Orazio Romeo<sup>c</sup>, Rodrigo Almeida-Paes<sup>a</sup>, Célia Pais<sup>c</sup>, Nelson Lima<sup>b,d</sup>, Rosely Maria Zancopé-Oliveira<sup>a</sup>

<sup>a</sup> Laboratório de Micologia, Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, RJ, Brazil  
<sup>b</sup> CEB-Centre of Biological Engineering, Micoteca da Universidade do Minho, Universidade do Minho, Campus de Gualtar, Braga, Portugal  
<sup>c</sup> Centre of Molecular and Environmental Biology (CBMA), Department of Biology, Universidade do Minho, Braga, Portugal  
<sup>d</sup> Programa de Pós-Graduação em Microbiologia Agrícola, Universidade Federal de Lavras, Lavras, MG, Brazil  
<sup>\*</sup> Department of Environmental and Biological Sciences, University of Messina, Messina, Italy

Received 7 September 2014; accepted 15 December 2014

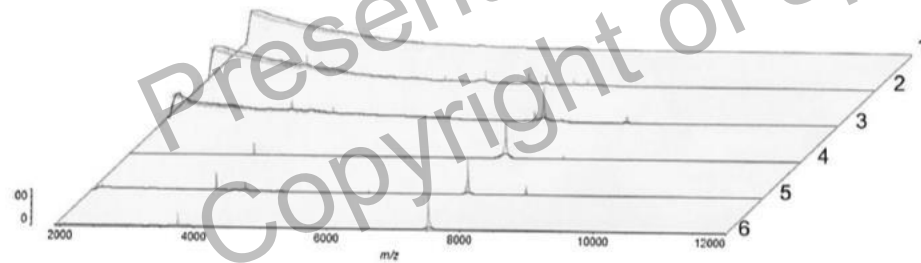


Fig. 4. Characteristic mass spectra of reference strains of the *Sporothrix* complex obtained by MALDI-TOF MS with the CHCA matrix. (1) *S. luriei* CBS937.72, (2) *S. pallida* SPA8, (3) *S. mexicana* MUM11.02, (4) *S. schenckii* IPEC27722, (5) *S. globosa* IPEC27135 and (6) *S. brasiliensis* CBS120339/IPEC16490.

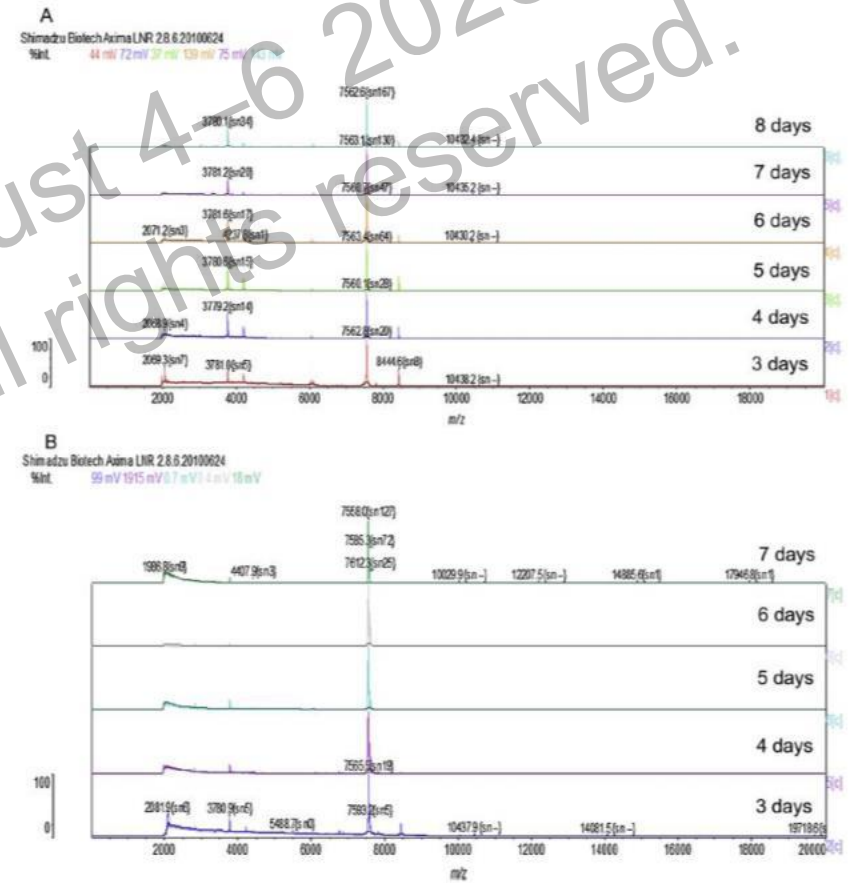


Fig. 2. The influence of growth time of *Sporothrix* yeast cells on the obtained spectra. (A) Mass spectra of *S. globosa* (IPEC27135) at various times after inoculation (3–8 days) obtained by MALDI-TOF MS with the CHCA matrix. (B) Mass spectra of *S. globosa* (IPEC27135) at various times after inoculation (3–7 days) obtained by MALDI-TOF MS with the DHB matrix. The other tested species showed similar results.

# Molecular diagnostic methods: MLST+AFLP

ITS = Internal transcribed spacer

CAL = Calmodulin

P7 = Elongation Factor 3

PSS3 = Elongation Factor 1

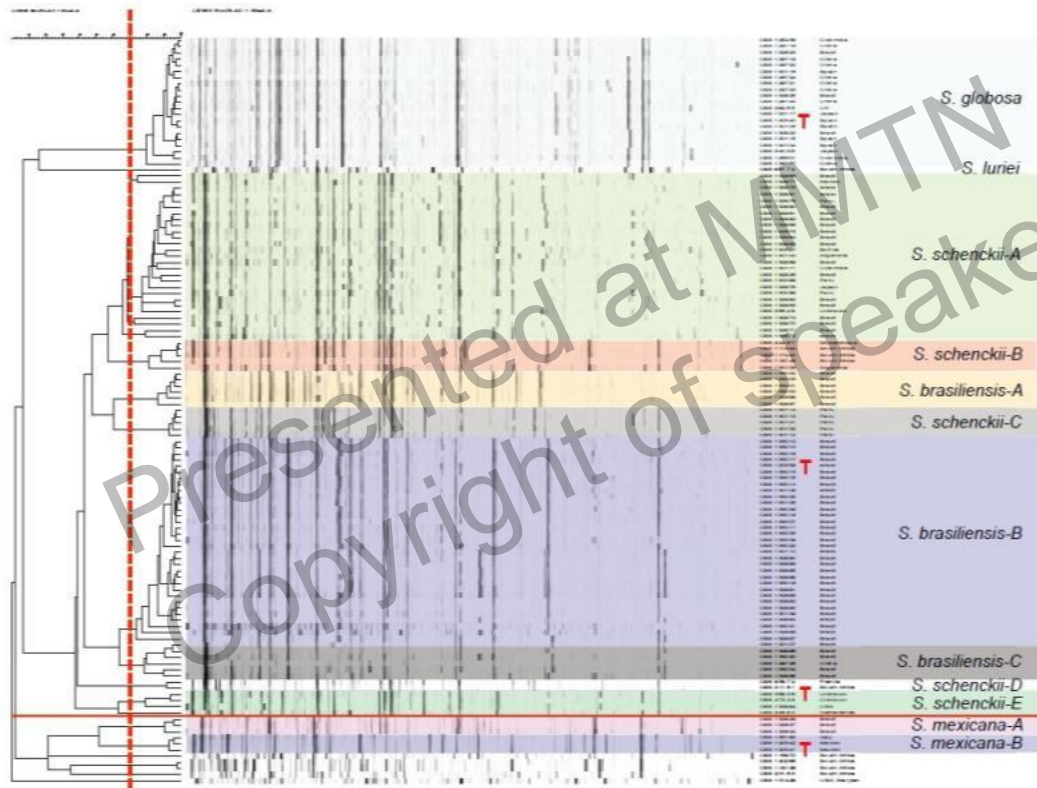


Fig. 4 Amplified fragment length polymorphism (AFLP) profiles of 122 strains of *Sporothrix*. Clustering of AFLP banding pattern of isolates of *Sporothrix* was done by UPGMA. Red vertical bars represents cut-off for distinction of clusters. Strains of *S. mexicana* and below are phylogenetically unrelated.

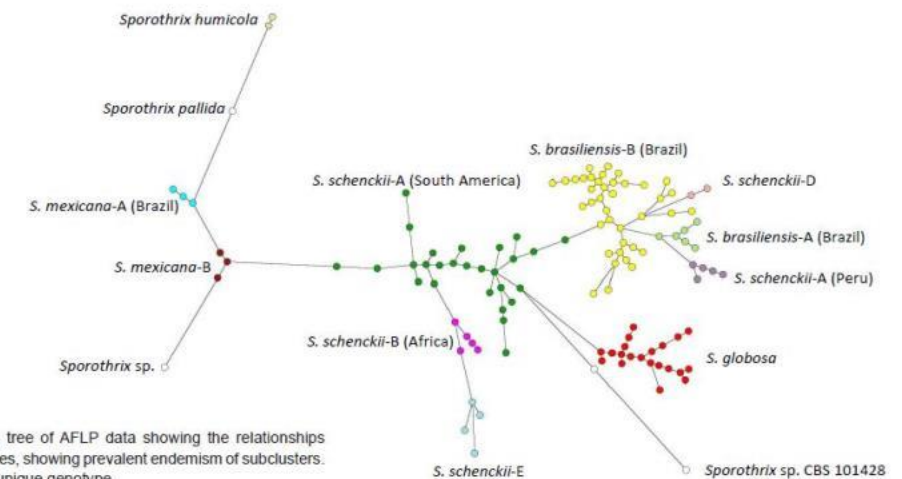


Fig. 5 Minimum spanning tree of AFLP data showing the relationships among 135 *Sporothrix* isolates, showing prevalent endemism of subclusters. Each dot corresponds to a unique genotype.

# WGS analysis

GBE

## Whole-Genome Sequencing and *In Silico* Analysis of Two Strains of *Sporothrix globosa*

Lilin Huang,<sup>1,†</sup> Wenchao Gao,<sup>1,†</sup> Domenico Giosa,<sup>2</sup> Giuseppe Criseo,<sup>3</sup> Jing Zhang,<sup>1,4</sup> Tailong He,<sup>1</sup> Xiaowen Huang,<sup>5</sup> Jiufeng Sun,<sup>6</sup> Yao Sun,<sup>1</sup> Jiamin Huang,<sup>1</sup> Yungqing Zhang,<sup>1</sup> Balazs Brankovics,<sup>7</sup> Fabio Scordino,<sup>2</sup> Enrico D'Alessandro,<sup>8</sup> Anne van Diepeningen,<sup>7</sup> Sybren de Hoog,<sup>7</sup> Huaiqiu Huang,<sup>1,\*</sup> and Orazio Romeo<sup>2,3,\*</sup>

<sup>1</sup>Department of Dermatology and Venereology, the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

<sup>2</sup>IRCCS Centro Neurolesi "Bonino-Pulejo", SS113, Messina, Italy

<sup>3</sup>Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Messina, Italy

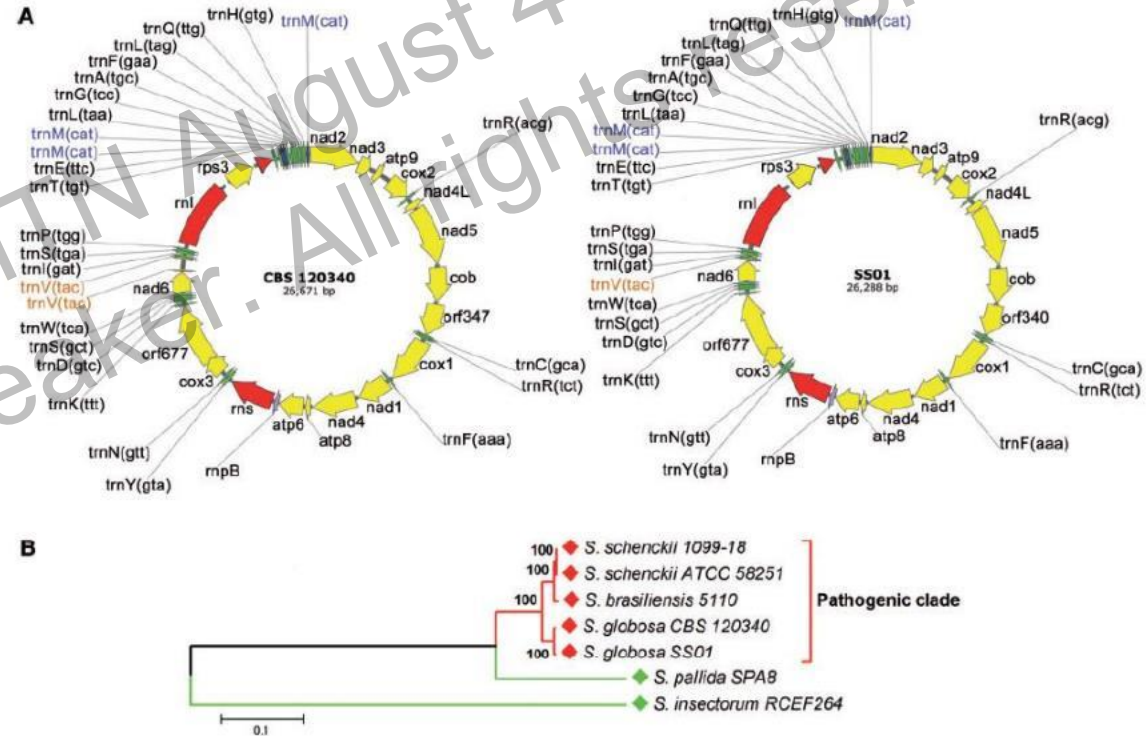
<sup>4</sup>Department of Dermatology and Venereology, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangdong Province, China

<sup>5</sup>Department of Dermatology, General Hospital of Guangzhou Military Command of PLA, Guangzhou, China

<sup>6</sup>Guangdong Provincial Center for Disease Control and Prevention, Guangzhou, Guangdong, China

<sup>7</sup>CBS-KNAW Fungal Biodiversity Centre, Utrecht, The Netherlands

<sup>8</sup>Department of Veterinary Sciences, Division of Animal Production, University of Messina, Messina, Italy



# Update on treatment

## Clinical Practice Guidelines for the Management of Sporotrichosis: 2007 Update by the Infectious Diseases Society of America

Carol A. Kauffman,<sup>1</sup> Beatriz Bustamante,<sup>4</sup> Stanley W. Chapman,<sup>2</sup> and Peter G. Pappas<sup>3</sup>

456

中华皮肤科杂志2016年7月第49卷第7期 Chin J Dermatol, July 2016, Vol. 49, No. 7

·指南与共识·

### 孢子丝菌病诊疗指南

中华医学会皮肤性病学分会真菌学组;中国医师协会皮肤科医师分会医学真菌亚专业委员会;

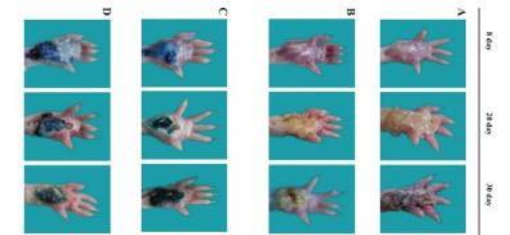
中西医结合学会皮肤性病专业委员会真菌学组

通信作者:李若瑜, Email: mycolab@126.com

DOI: 10.3760/cma.j.issn.0412-4030.2016.07.002



warm moxibustion



frontiers  
in Pharmacology

ORIGINAL RESEARCH  
published: 27 February 2014  
doi: 10.3389/fph.2014.00002

### Efficient Treatment of *Sporothrix globosa* Infection Using the Antibody Elicited by Recombinant Phage Nanofibers

Feng Chen<sup>1</sup>, Ribin Jiang<sup>2</sup>, Shuai Dong<sup>3</sup> and Bailing Yao<sup>4</sup>\*

<sup>1</sup>Department of Dermatology, China-Japan Union Hospital of Jilin University, Changchun, China, <sup>2</sup>Department of Immunology and Parasitology, The First Hospital of Jilin University, Changchun, China, <sup>3</sup>Department of Emergency, The First Hospital of Jilin University, Changchun, China, <sup>4</sup>Department of Emergency, The First Hospital of Jilin University, Changchun, China

Cutaneous Sporotrichosis Treated with Photodynamic Therapy: An in Vitro and in Vivo Study. Photomed Laser Surg. 2014;32(1):54-57.

# Antifungal susceptibility

	AMB	FLU	ITC	VRC	PCZ	CAS	TRB
<i>S. schenckii</i> (39/61)	R	R	S	R	S	R	S
<i>S. brasiliensis</i> (22/23)	R	R	S	R	S	I	S
<i>S. globosa</i> (4/4)	I	R	0.5- >16	2->16	0.5-16	R	0.01-0.06
<i>S. mexicana</i> (3/0)	R	R	2->16	1->16	1->16	R	ND

**\* No validated MIC breakpoints**

Rodrigues AM, et al. *BMC Infect Dis* 2014  
 Ottonelli Stopiglia CD, et al *Med Mycol* 2014  
 Mahmoudi S, et al *Med Mycol* 2016

# Susceptibility of *Sporothrix* to common antifungal drugs

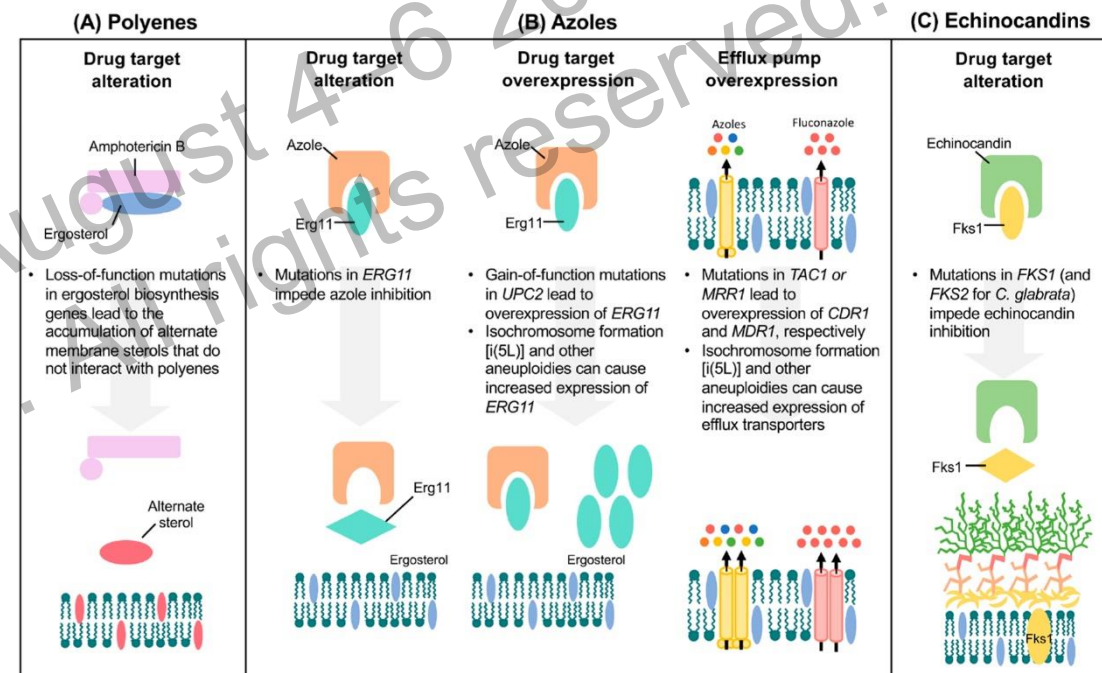
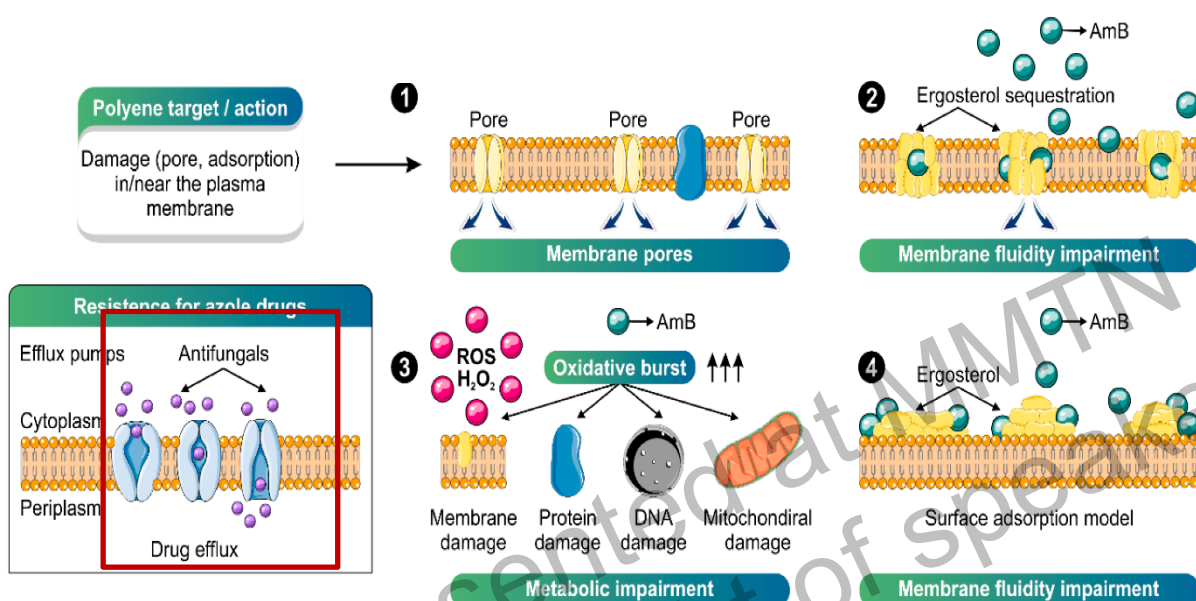
Table 1. In vitro antifungal activity against pathogenic *Sporothrix* species.

	In Vitro Antifungal Activity <sup>a</sup>			Reference
	High (MIC ≤ 1 µg/mL)	Moderate (1 < MIC ≤ 4 µg/mL)	Low (MIC > 4 µg/mL)	
<b>Polyenes</b>				
Amphotericin B	■			[262]
<b>Azoles</b>				
Albaconazole				[286]
Clotrimazole		■		[287]
Eberconazole		■		[286]
Fluconazole			■	[286]
Itraconazole	■			[262]
Isavuconazole				[288]
Ketoconazole	■			[262]
Miconazole		■		[286]
Posaconazole	■			[262]
Ravuconazole		■		[286]
Voriconazole			■	[262]
<b>Allylamines</b>				
Terbinafine	■			[262]
Naftifine		■		[289]
<b>Echinocandins</b>				
Anidulafungin		■		[286]
Caspofungin			■	[286]
Micafungin			■	[286]
<b>Pyrimidine</b>				
Flucytosine			■	[286]

<sup>a</sup> In vitro antifungal activity is determined according to MIC values obtained by the microdilution technique [271,272].



# The resistance mechanisms



Overexpression of the efflux pumps

Overexpression or mutation of target enzyme

Reviews in Medical Microbiology. 2021; 32(4):p 219-227.  
 Braz J Microbiol. 2021;52(1):73-80.  
 Chem Rev. 2021;121(6):3390-3411.

# Recommended treatment regimen

- Itraconazole: 200-400 mg/day (divided into two divided doses)
- Terbinafine: 250-500 mg/day (divided into two divided doses)
- Fluconazole: 400-800 mg/day
- Combination therapy
  - Thermotherapy
  - Surgical

Treatment course: 3-6 months

- Other new antifungal drugs: new triazoles
- Surgical therapy: single lesion or bone damage
- Physical therapy (eg, warm, freezing)
- Photodynamic therapy

# Treatment with itraconazole



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# Treatment with itraconazole

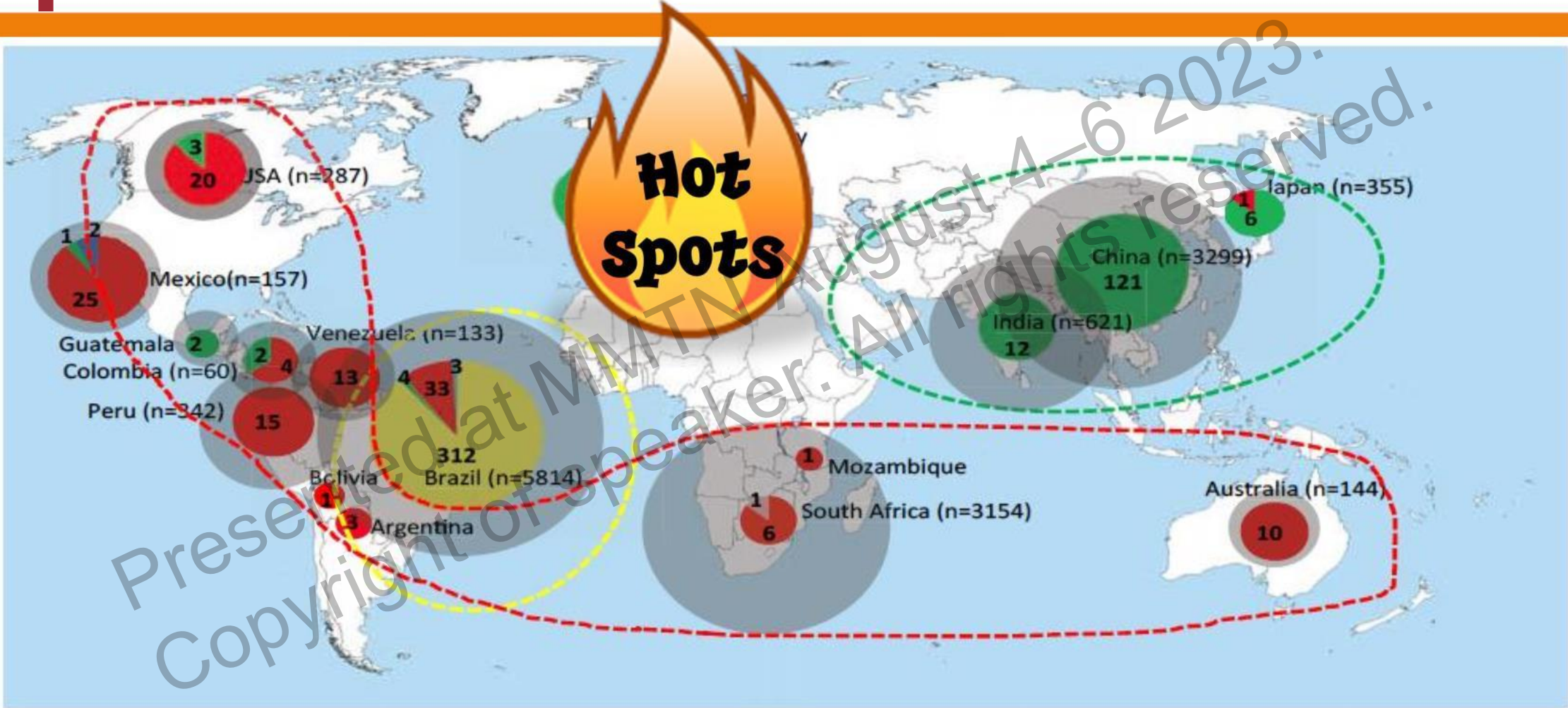


## Treatment with itraconazole combining terbinafine



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# Work together to control or elimination sporotrichosis



● Sb ● Ss ● Sg ● Sm ● Sl

# Summary

- Sporotrichosis is a chronic inflammatory granulomatous disease caused by dimorphic fungus *Sporothrix*, which may have geographic difference ;
- Transmission from plant, animal are the major infected sources;
- With the deepening of serology, immunology and molecular biology research, a series of rapid diagnostic methods have emerged, such as ELISA, PCR etc;
- Common antifungal drugs for sporotrichosis include itraconazole, terbinafine, amphotericin B and the combination of them;



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MEDICAL MYCOLOGY  
TRAINING NETWORK

**Thank you for your attention!**



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