Lessons from Fungal Outbreaks

# 侵襲性黴菌感染:從美國黴菌中樞神經感染群突發之省思 (I)

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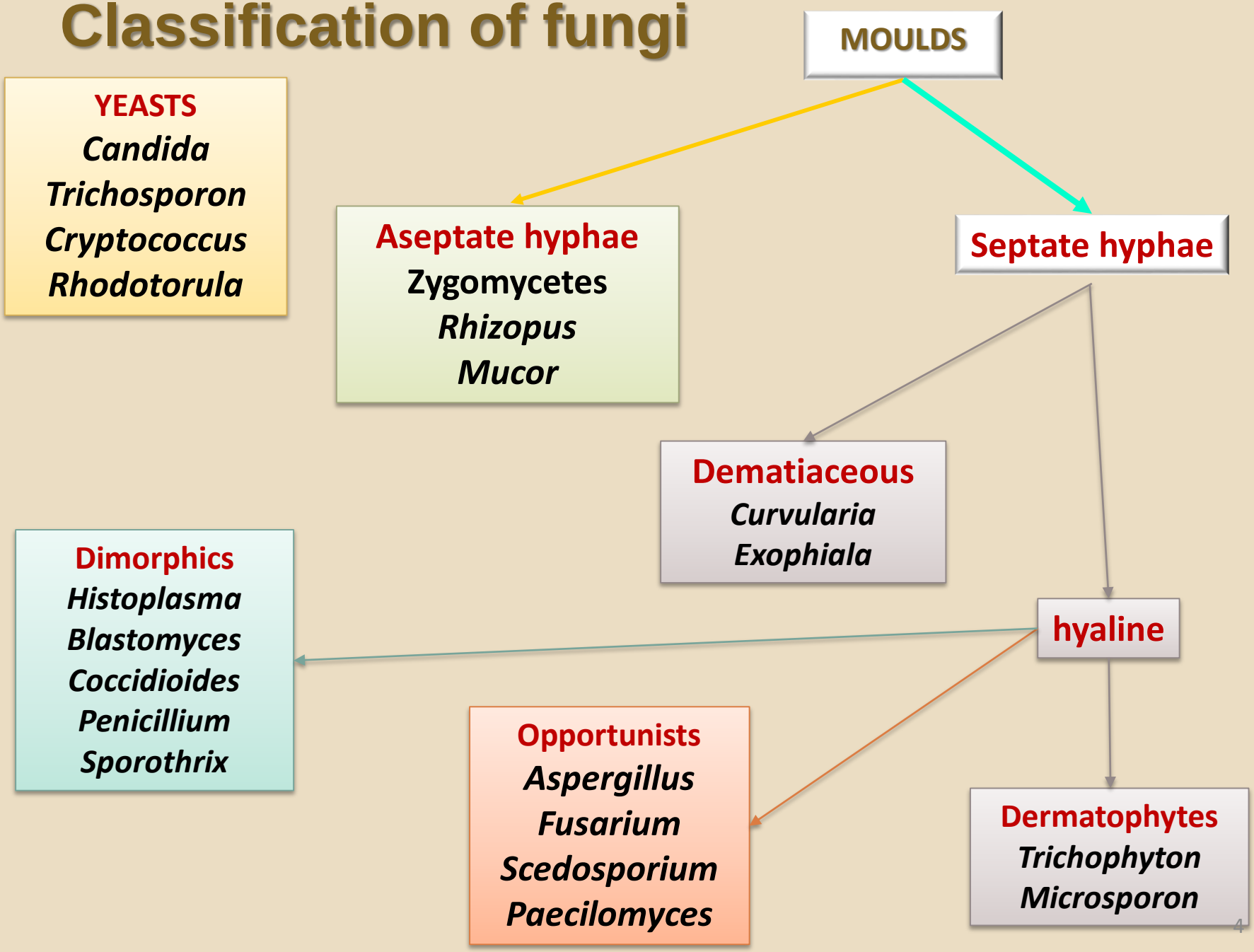
Conclusion

# 1. Hidden killers

# Classification of fungi



# Hidden Killers: Human Fungal Infections
# Ten most significant invasive fungal infections

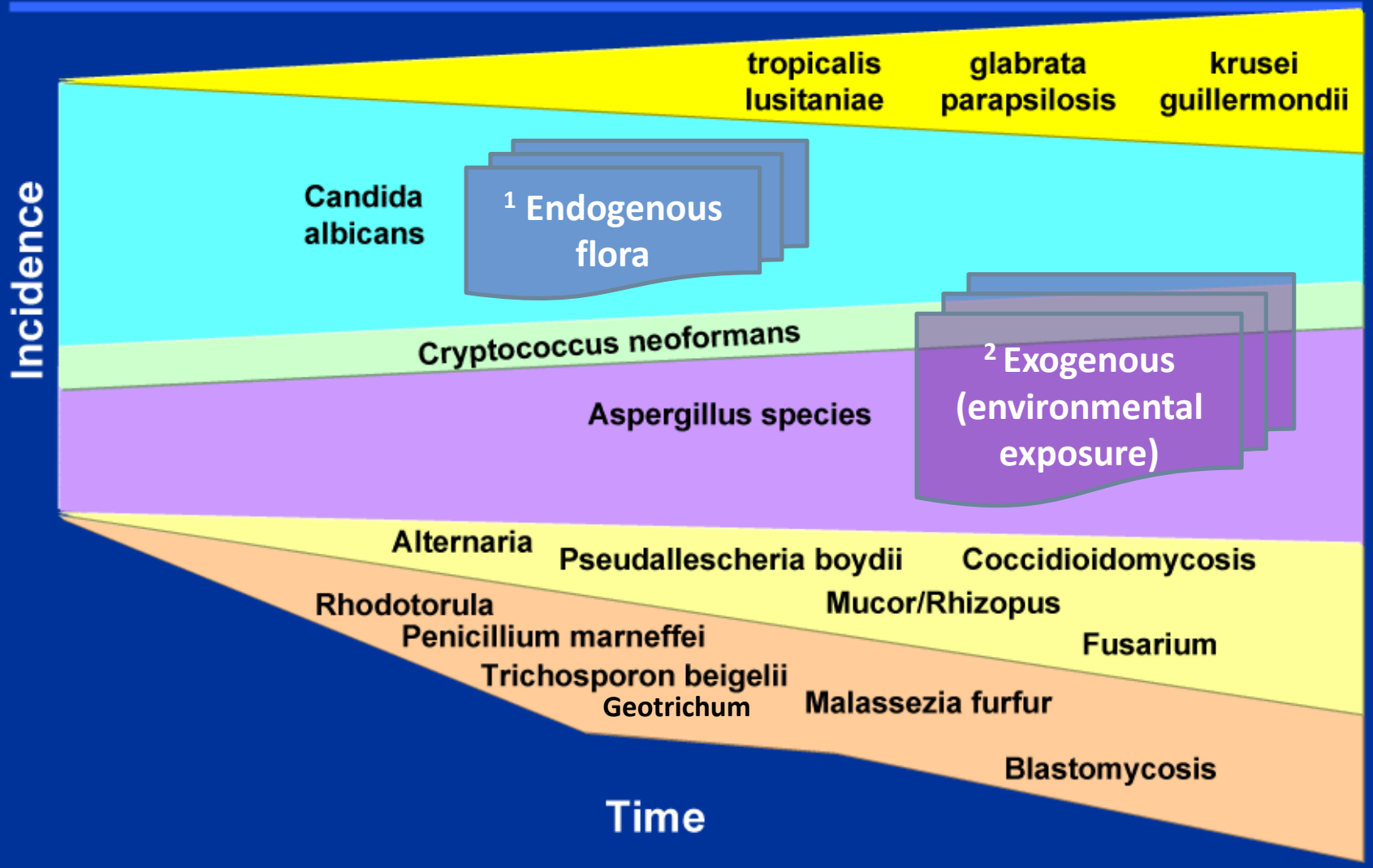
| Disease (most common species) | Location | Estimated life-threatening infections/ year at that location* | Mortality rates (% in infected populations)* |
|---|---|---|---|
| Opportunistic invasive mycoses | | | |
| Aspergillosis (*Aspergillus fumigatus*) | Worldwide | >200,000 | 30–95 |
| Candidiasis (*Candida albicans*) | Worldwide | >400,000 | 46–75 |
| Cryptococcosis (*Cryptococcus neoformans*) | Worldwide | >1,000,000 | 20–70 |
| Mucormycosis (*Rhizopus oryzae*) | Worldwide | >10,000 | 30–90 |
| Pneumocystis (*Pneumocystis jirovecii*) | Worldwide | >400,000 | 20–80 |
| Endemic dimorphic mycoses*† | | | |
| Blastomycosis (*Blastomyces dermatitidis*) | Midwestern and Atlantic United States | ~3,000 | <2–68 |
| Coccidioidomycosis (*Coccidioides immitis*) | Southwestern United States | ~25,000 | <1–70 |
| Histoplasmosis (*Histoplasma capsulatum*) | Midwestern United States | ~25,000 | 28–50 |
| Paracoccidioidomycosis (*Paracoccidioides brasiliensis*) | Brazil | ~4,000 | 5–27 |
| Penicilliosis (*Penicillium marneffei*) | Southeast Asia | >8,000 | 2–75 |

*Most of these figures are estimates based on available data, and the logic behind these estimates can be found in the text and in the Supplementary Materials. †Endemic dimorphic mycoses can occur at many locations throughout the world. However, data for most of those locations are severely limited. For these mycoses, we have estimated the infections per year and the mortality at a specific location, where the most data are available.

Brown GD, et al. Sci Transl Med 2012;4

EORTC
IFICG

# 'New' Arrivals in the Fungal Assortment



# Environmental risk factors for mould-related diseases in immunocom-promised patients

- ✓**Risk assessment**
- ✓**Patient education**

Pagano et al. J Antimicrob Chemother 2011; 66 Suppl 1: i5

Seasonal incidence

Weather variation
- temperature
- rainfall
- humidity
- wind speed

Personal habits
- smoking
- living in countryside
- fungus exposure
- type of work (e.g. farmer, agriculture)

Exposure outside
- pets
- dusty household
- construction work

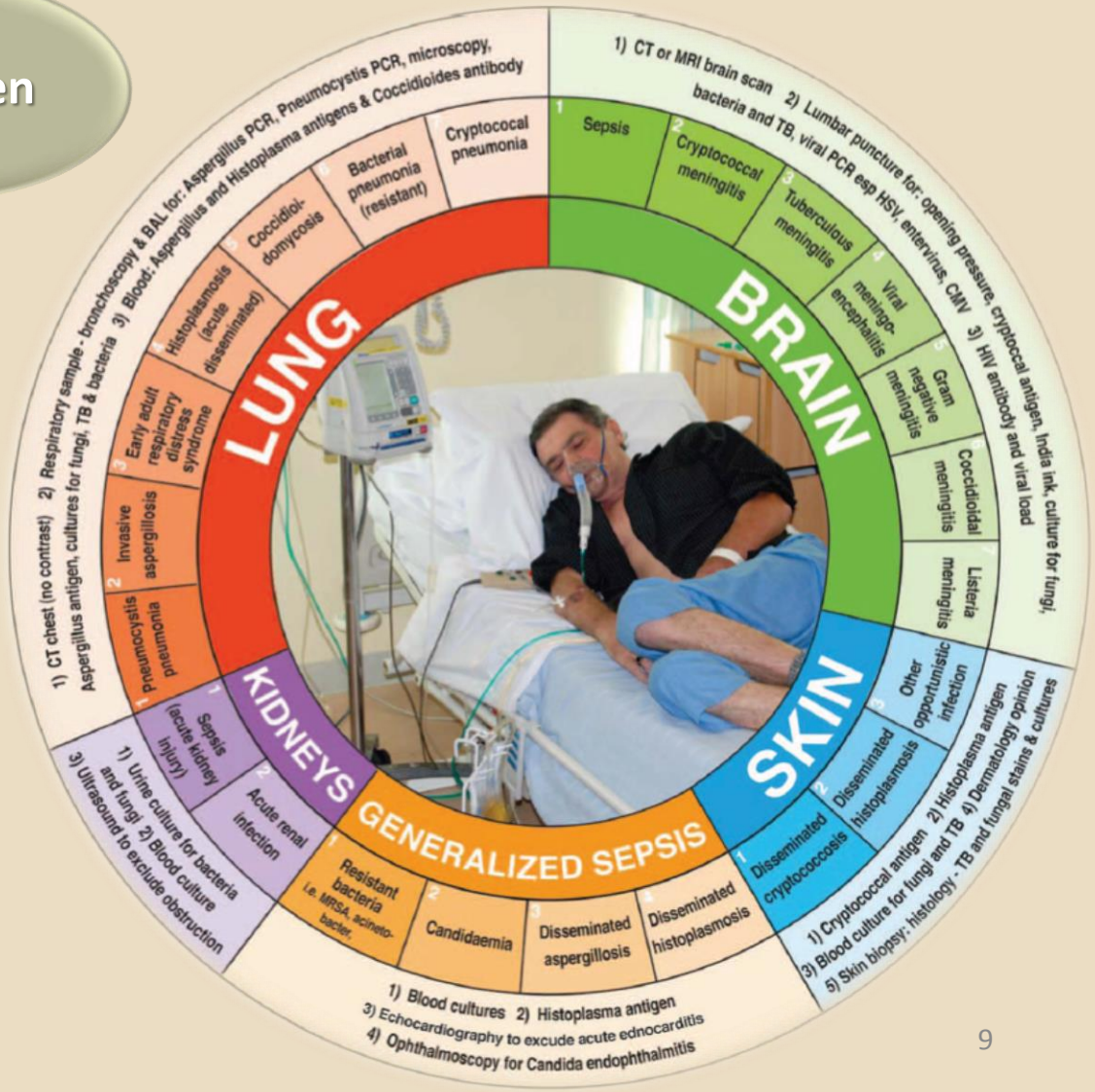
Exposure inside
- potted plants
- absence of HEPA-filtered rooms
- water

HEPA, high-efficiency particulate air.

# Diagnostic dilemma

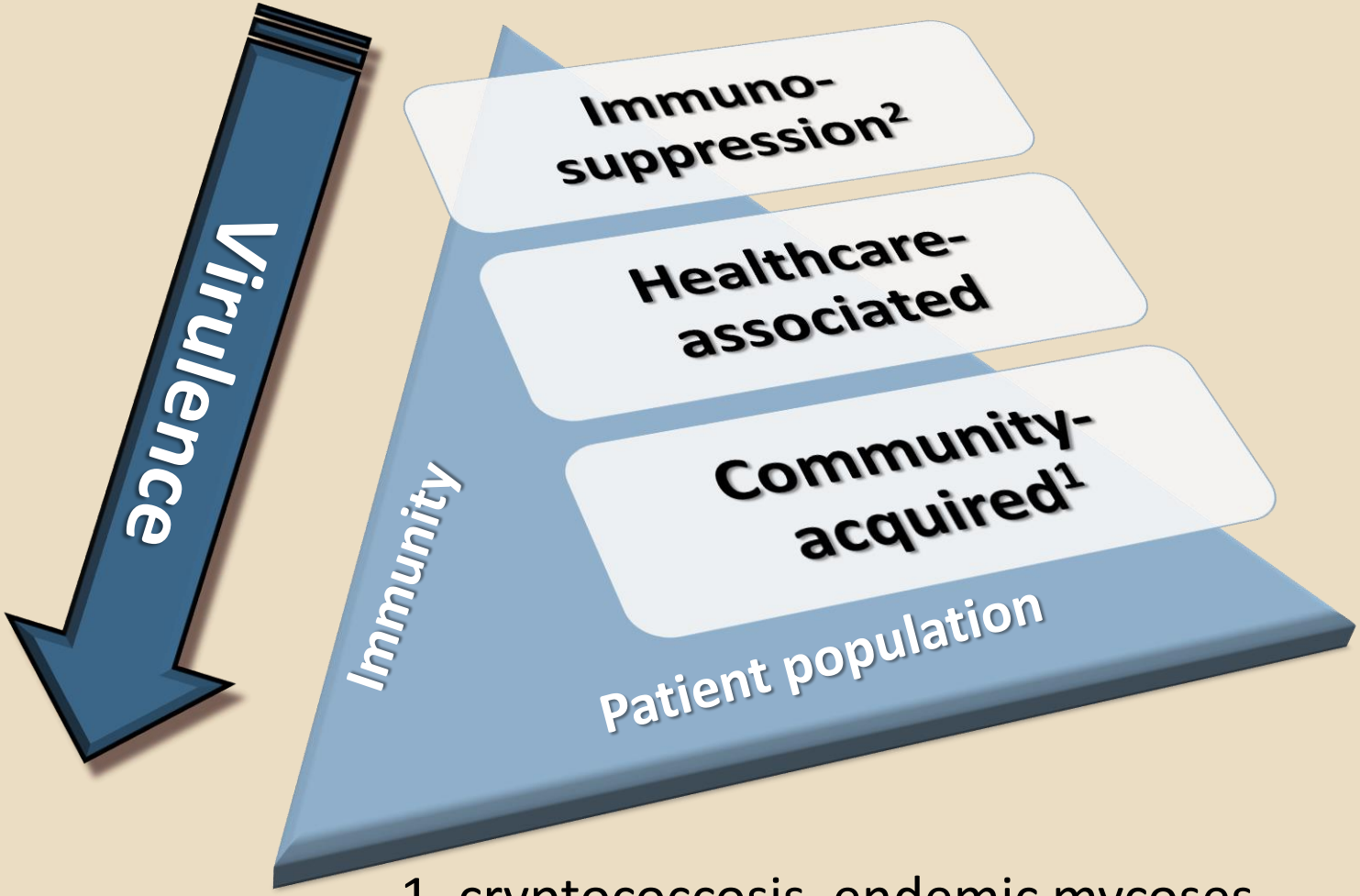
Host + Pathogen

Contamination
Colonization
Infection/disease



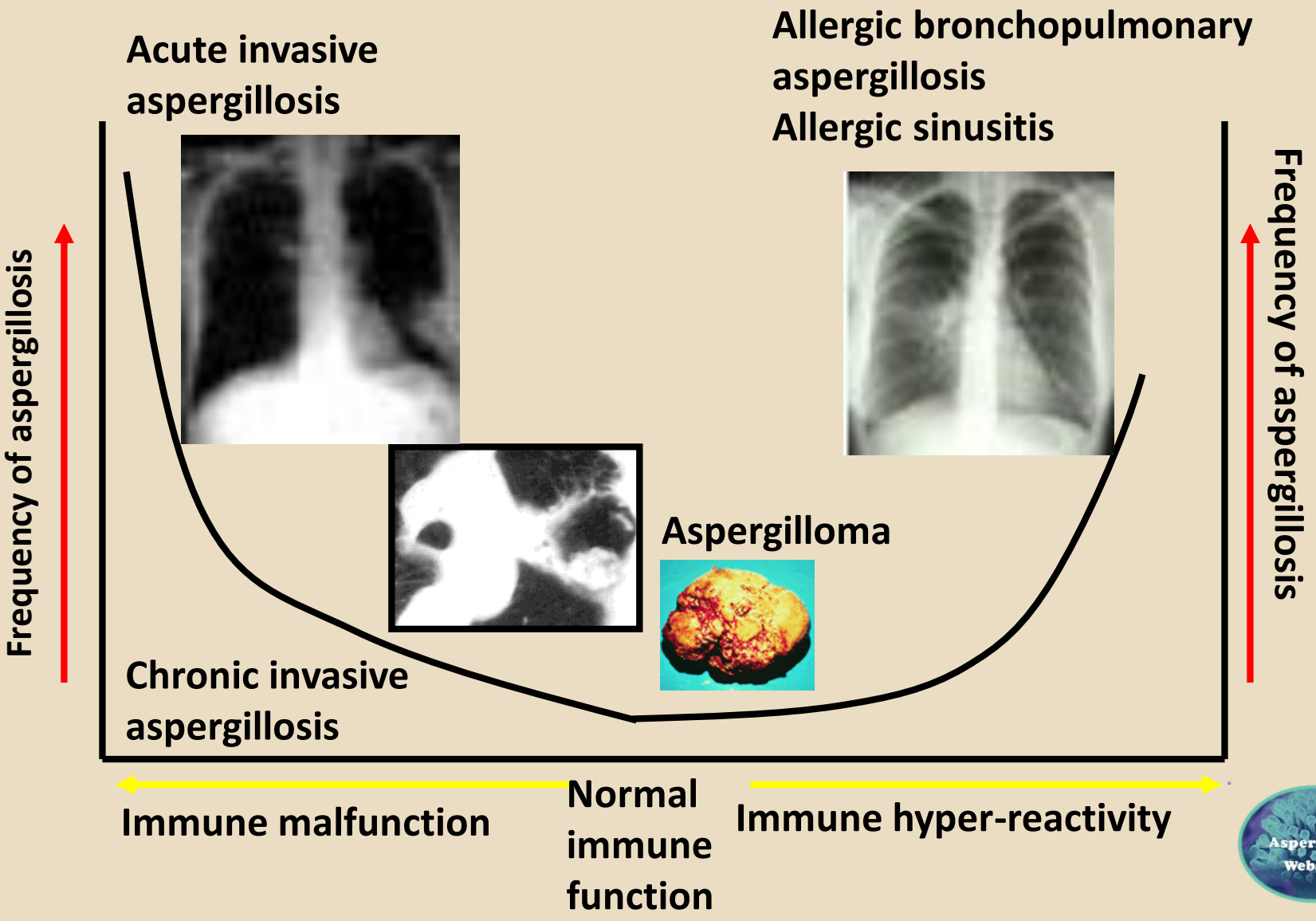

Sci Transl Med 2012;4

# Also due to different cross talk between human and fungi




1. cryptococcosis, endemic mycoses
2. opportunistic: aspergilosis, mucormycosis

# Type of infection and immune status



# Host and pathogens

**Previously healthy (male):** ***Cryptococcus***

**Diabetes:** ***Candida,*** **Zygomycetes** ***(Aspergillus)***

**Steroid:** ***Aspergillus***

**Hematologic malignancies, HSCT:**
***Candida*****,** ***Aspergillus*****, Zygomycetes,**
***Fusarium, Trichosporon, etc.***

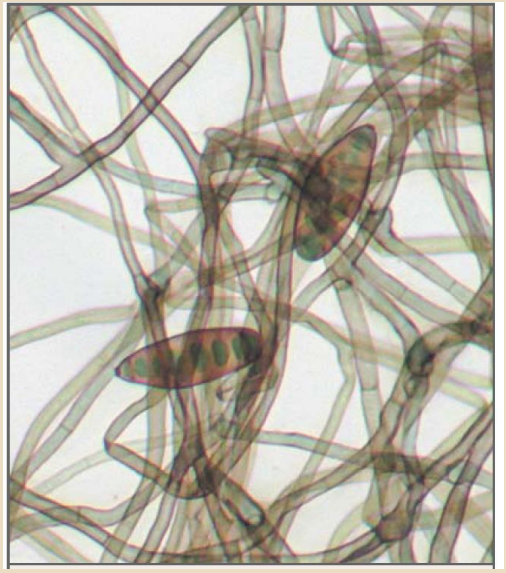
**AIDS:** ***Cryptococcus, Penicillium;***
**Steroid, monoclonal antibody……**

**Healthcare-associated:**
***Candida***

# Fungi and failing hosts

| Candidiasis | Aspergillosis | Mucormycosis |
|---|---|---|
| Postsurgical ICU | Neutropenia | Neutropenia |
| Neutropenia | Organtransplant | Organtransplant |
| Parenteral nutrition | Burns | Burns |
| Burns | Corticosteroids | Diabetes |
| Neonates | Chronic granulo matous disease | IV drug abuse |
| Corticosteroids | COPD | |
| IV drug abuse | | |

| 2-year survival (IFD+host) | | |
|---|---|---|
| 40% | 10% | 5% |



The current *Exserohilum rostratum* epidemic and other unsuspected outbreaks of fungal disease provide many new lessons and raise many questions...”

# 2. US Fungal meningitis outbreak

Recognize the first signal and distinguish from noises

# The initiative – the key!

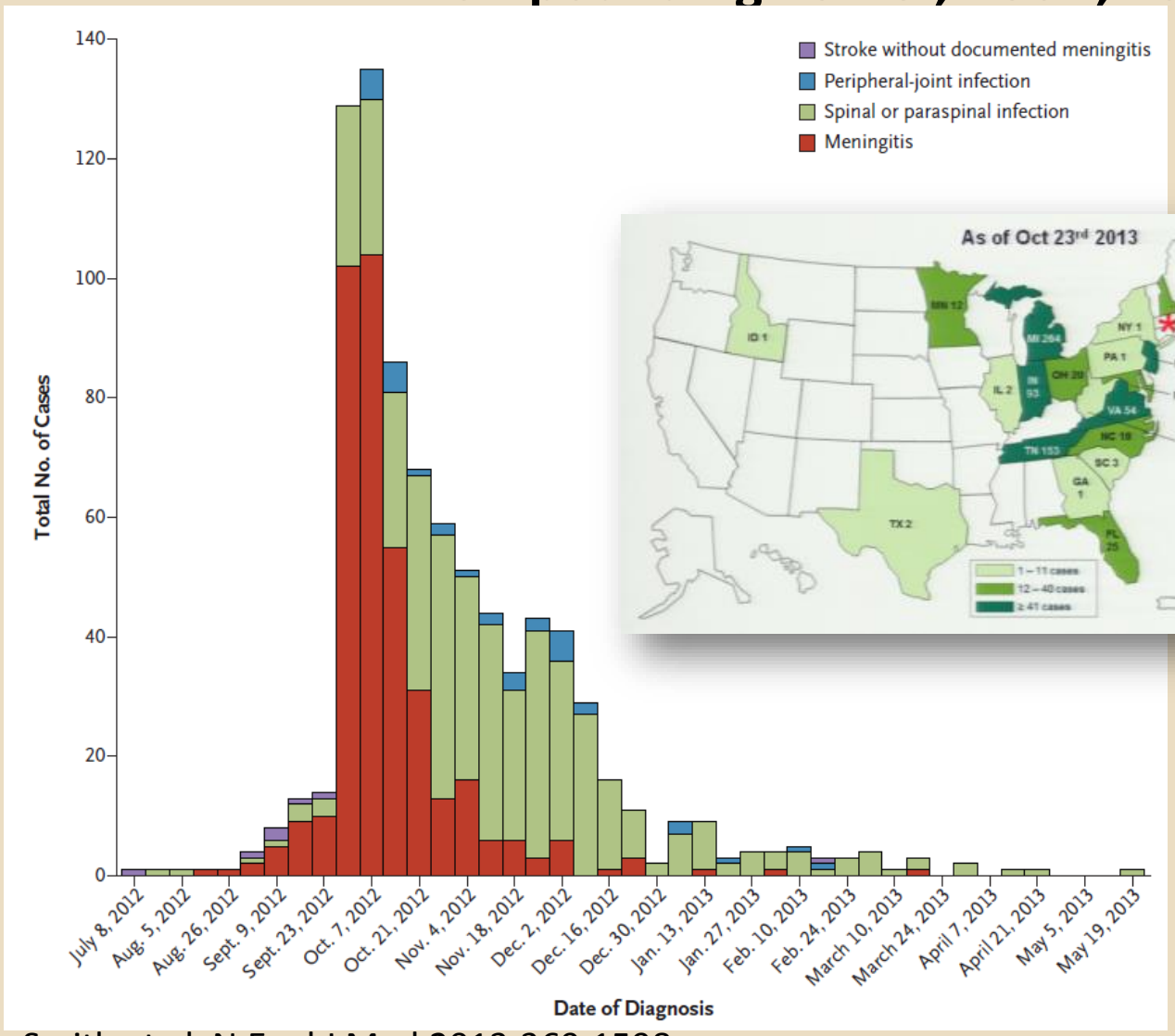
- **Meningitis due to *Aspergillus fumigatus* in an immunocompetent man who had no evidence of sinopulmonary or cutaneous disease**
- **An epidural glucocorticoid injection was identified as a potential route of entry for this organism into the central nervous system,**
- **the case was reported to the state health department.**

| **Cerebrospinal fluid** | | | | | | |
|---|---|---|---|---|---|---|
| Source of sample | L4–L5 | L3–L4 | L3–L4 | EVD | EVD | EVD |
| Opening pressure (cm of water) | | 33 | 24 | >30 | | |
| Protein (mg/dl)† | 147 | 319 | 247 | 193 | 93 | 80 |
| Glucose (mg/dl)‡ | 31 | 2 | 1 | 63 | 50 | 59 |
| White cells (per mm$^3$) | 2304 | 4422 | 5863 | 14 | 27 | 341 |
| Polymorphonuclear cells (%) | 72 | 89 | 92 | 71 | 90 | 97 |
| Lymphocytes (%) | 23 | 4 | 2 | 21 | 4 | 2 |
| Red cells (per mm$^3$) | 3 | 34 | 21 | 2225 | 2850 | 14,700 |
| Gram's staining | No bacteria | No bacteria | No bacteria | No bacteria | No bacteria | No bacteria |
| Bacterial culture | No growth | No growth | No growth | No growth | No growth | No growth |
| Fungal culture | Not performed | *Aspergillus fumigatus*§ | No growth to date | No growth to date | | No growth to date |
| Aspergillus antigen index | 9.14¶ | 9.52¶ | 9.51¶ | | | 9.65 |
| **Serum** | | | | | | |
| Glucose (mg/dl) | 108 | 109 | 107 | 147 | 127 | 139 |
| Aspergillus antigen index | | | 0.23‖ | | | |



Pettit et al. N Engl J Med 2012;367:2119

# *Exserohilum rostratum* outbreak linked to contaminated methylprednisolone injections produced by the New England Compounding Center,* USA, 2012




**751** (**5.36%**) of 14,000 potentially exposed persons has developed clinically apparent disease in 20 states, with **64 deaths (8.5%).**

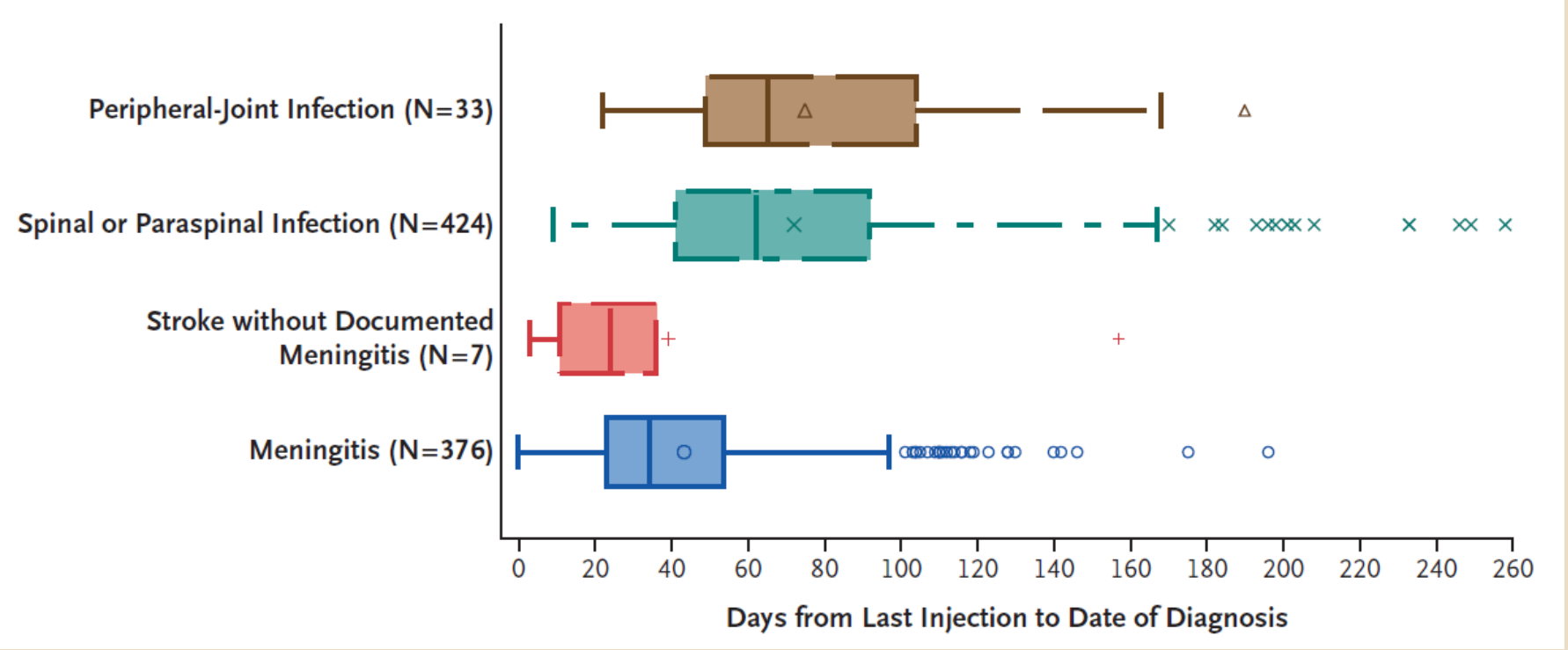
www.cdc.gov (accessed Nov 2013)

Smith et al. N Engl J Med 2013;369:1598

**Fungal infections associated with contaminated methylprednisolone**

# The median incubation period was 47 days

(range, 0 to 249)

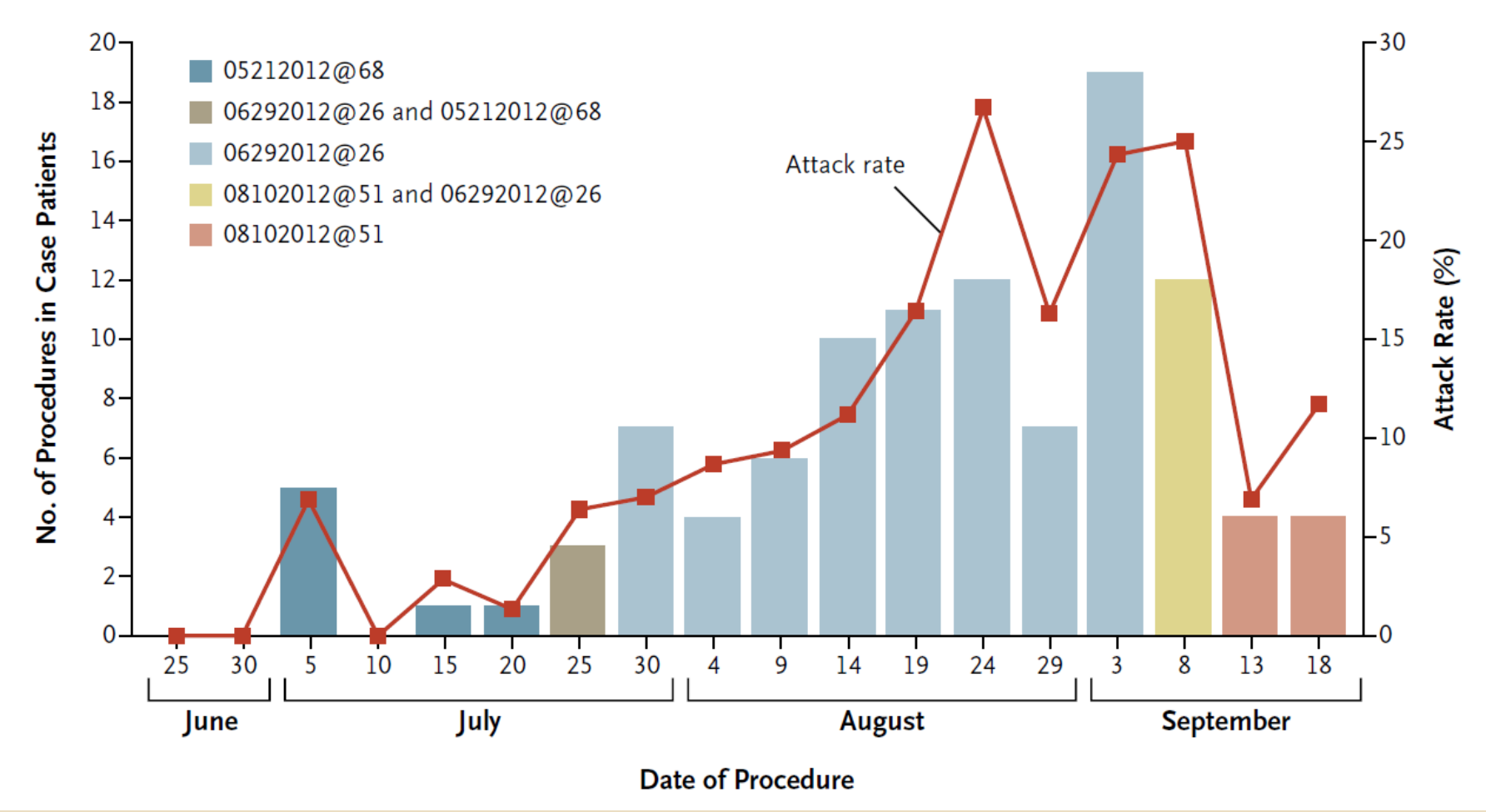





Smith et al. N Engl J Med 2013;369:1598

# Attack Rates varied by lots of product

**Number of Epidural and Paraspinal Glucocorticoid Injections and Attack Rate**






Kainer et al. N Engl J Med 2012;6;367:2194

# Gap to identify the outbreak

# Etiological agents of cerebral phaeohyphomycosis

- Infection with a mold that has melanised (pigmented) hyphae
- 60 genera
- 100 species

- **Rare and unusual CNS fungal pathogens (contaminant?)**
- **Maintain high index of suspicion of unexpected findings**

| | Order | Number of cases |
|---|---|---|
| *Neofusicoccum mangiferae* | Botryosphaeriales | 1 |
| *Cladophialophora bantiana* | Chaetothyriales | >78 |
| *Exophiala asiatica* | Chaetothyriales | 1 |
| *Exophiala dermatitidis* | Chaetothyriales | >25 |
| *Exophiala jeanselmei* | Chaetothyriales | 1 |
| *Fonsecaea monophora* | Chaetothyriales | 2 |
| *Fonsecaea pedrosoi* | Chaetothyriales | 1 |
| *Rhinocladiella mackenziei* | Chaetothyriales | 21 |
| *Neoscytalidium dimidiatum* | Helotiales | 3 |
| *Acrophialophora fusispora* | Incertae sedis | 1 |
| *Ochroconis gallopavum* | Incertae sedis | 4 |
| *Bipolaris hawaiiensis* | Pleosporales | 2 |
| *Bipolaris spicifera* | Pleosporales | 2 |
| *Bipolaris* sp | Pleosporales | 1 |
| *Curvularia lunata* | Pleosporales | 4 |
| *Curvularia pallescens* | Pleosporales | 1 |
| *Dissitimurus exedrus* | Pleosporales | 1 |
| *Exserohilum rostratum* | Pleosporales | 1 |
| *Chaetomium atrobrunneum* | Sordariales | 3 |
| *Chaetomium globosum* | Sordariales | 1 |
| *Chaetomium perlucidum* | Sordariales | 1 |
| *Chaetomium strumarium* | Sordariales | 2 |
| *Phialemonium obovatum* | Sordariales | 1 |
| *Nodulisporium* sp | Xylariales | 1 |

*1. Dong Ming L, et al. Lancet Infect Dis 2009;9:376–383.*

# Diagnostic challenge

## Patients with Fungal Infections Associated with Contaminated Lots of Methylprednisolone Acetate

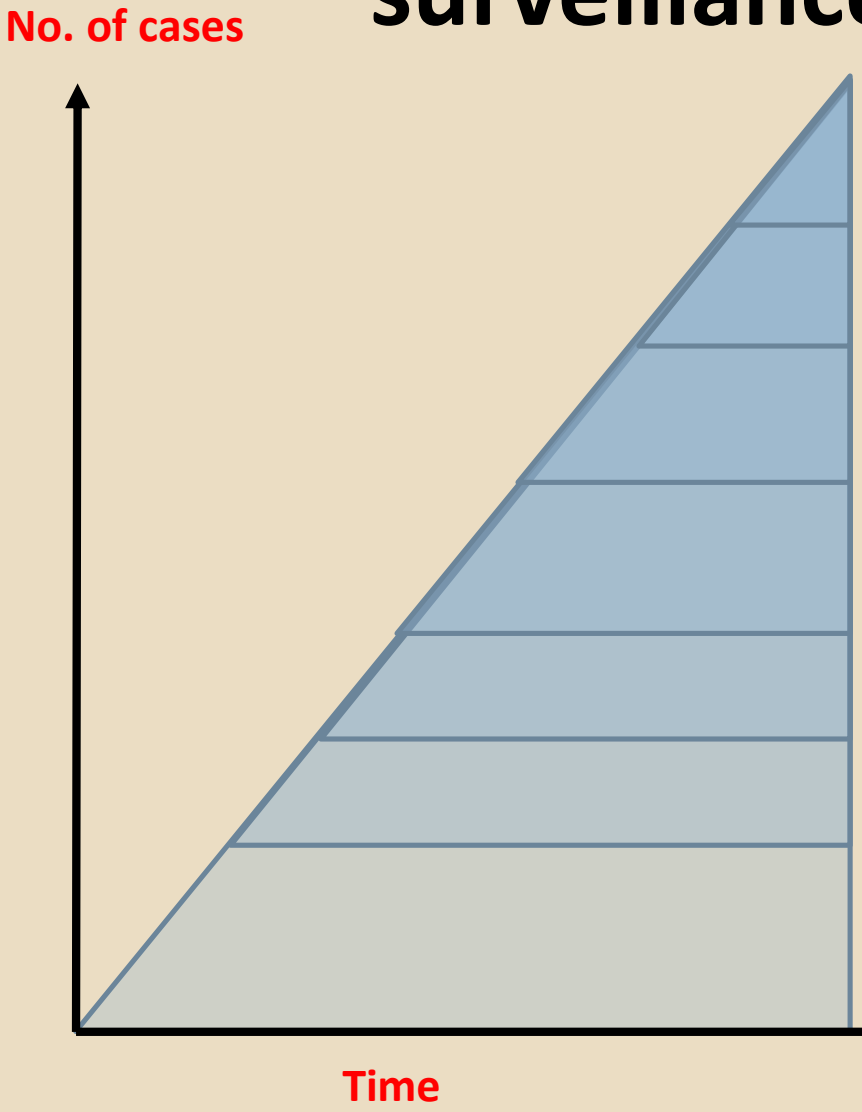
| Characteristic | All Cases† (N=728) | Meningitis Only (N=229) | Spinal or Paraspinal Infection Only (N=310) | Meningitis and Spinal or Paraspinal Infection (N=148) | Peripheral-Joint Infection Only (N=32) |
|---|---|---|---|---|---|
| Evidence of fungus — no. | 169 | 57 | 54 | 51 | 7 |
| Documented by PCR only | 85 | 30 | 18 | 33 | 4 |
| Documented by culture only | 33 | 12 | 16 | 5 | 0 |
| Documented by histopathological assessment only | 0 | 0 | 0 | 0 | 0 |
| Documented by >1 technique | 51 | 15 | 20 | 13 | 3 |
| Exserohilum species | 153 | 49 | 50 | 47 | 7 |



Smith et al. N Engl J Med 2013;369:1598

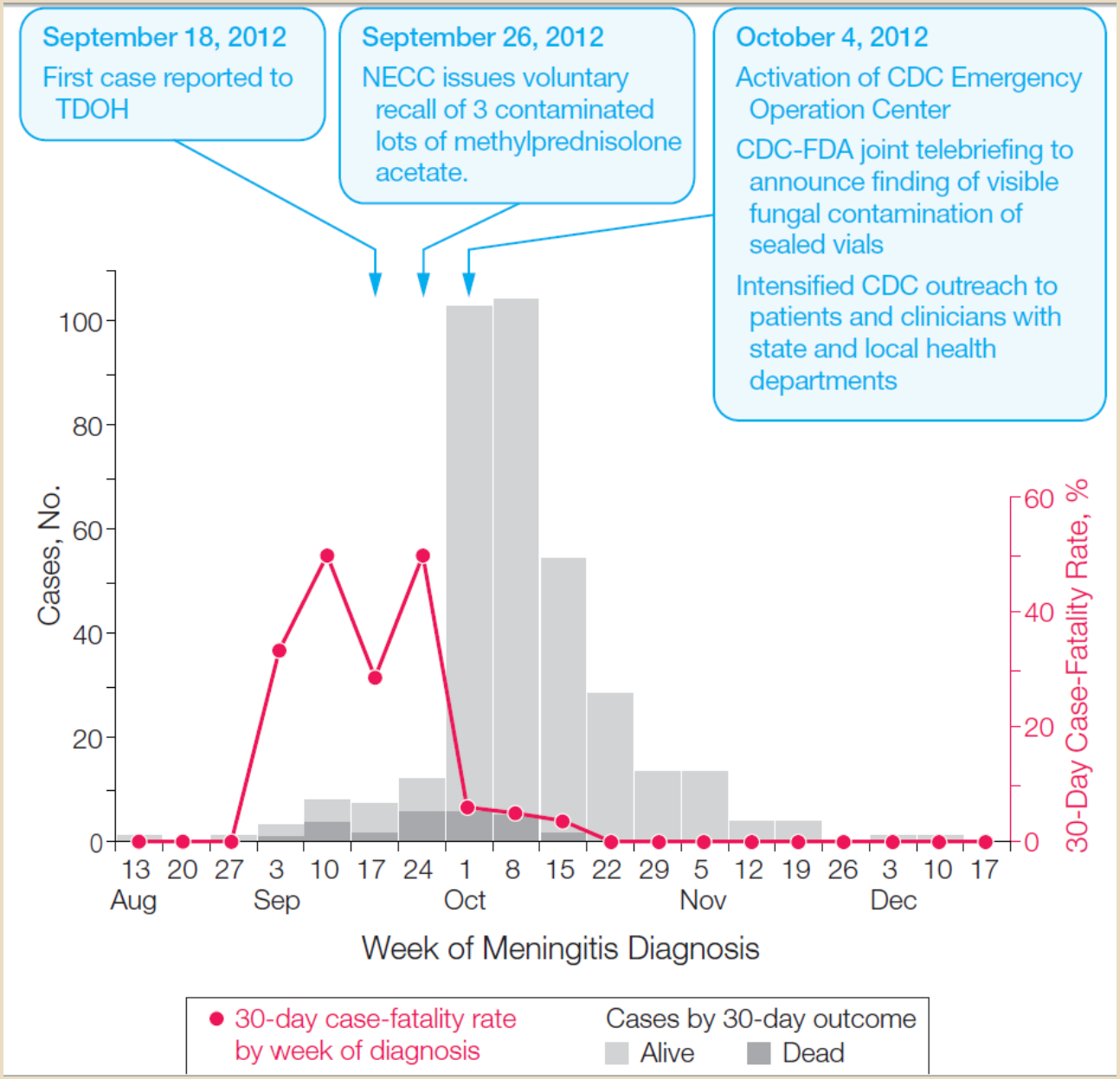
# Gap to identify the outbreak

# Pyramid and time lag of surveillance/case findings




- Case report
- Lab identification
- Collect specimen
- Clinicians alert
- Persons access to clinic
- Persons has symptoms
- Exposure

# The value of public health




# The value of public health

- Critical need for strong and sustained public health systems
- Multidiscipline partnerships essential
- Clinical (ID) networks of great benefit
- Need to modemize public health systems at all levels with latest technology
- Essential frontline defense of highly trained, flexible epidemiology and laboratory experts with ability to work across disciplines



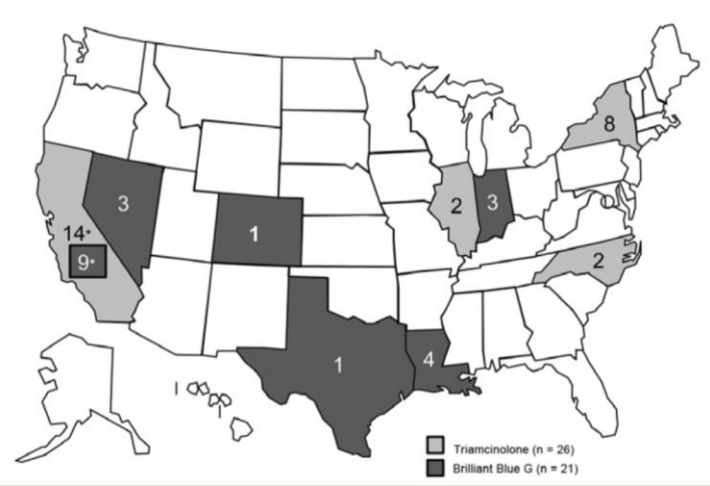
Bell & Khabbaz JAMA 2013;309:883

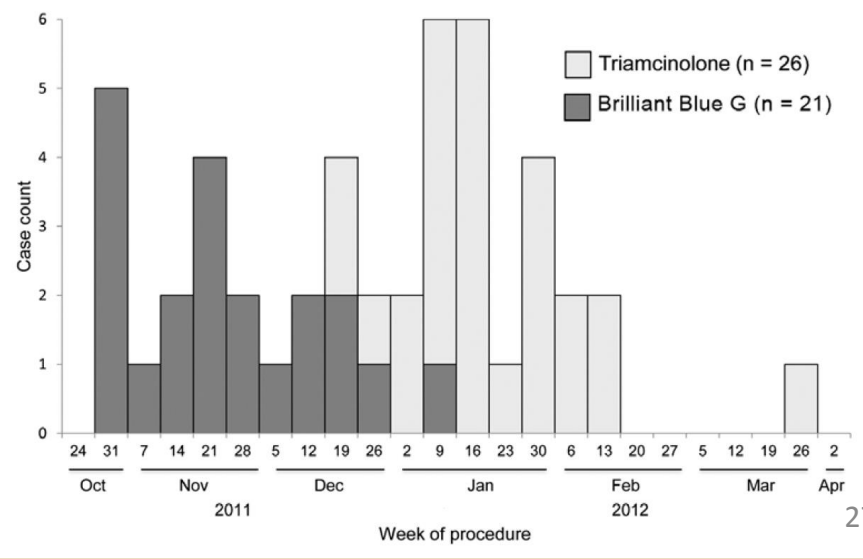
# Fungal endophthalmitis associated with compounded products

- Franck's Compounding Lab (Ocala, FL, USA)
- Etiologies (contaminated compounded products)

  *Fusarium incarnatum-equiseti* species complex (intraocular dye Brilliant Blue G (BBG) -exposed case-patients and an unopened BBG vial)

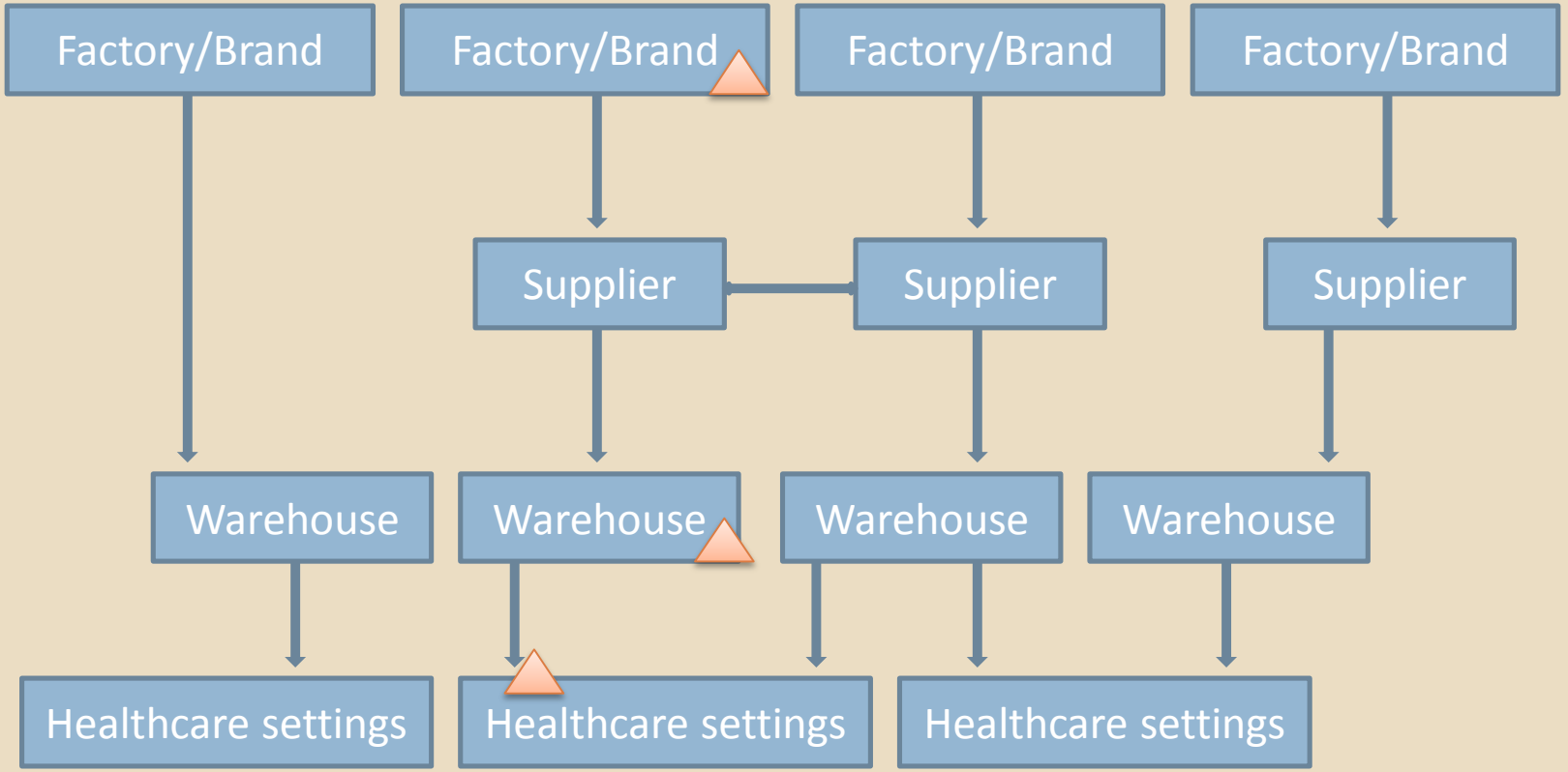
  *Bipolaris hawaiiensis* (intravitreal injection containing triamcinolone acetonide -exposed case-patients)
- 39 of 40 patients (98%) lost vision.




Mikosz et al. Emerg Infect Dis. 2014;20:248

# Schematic outline of the supply chain of hospital equipment




Elizabeth M. Johnson, Mycology Reference Laboratory, Public Health England, UK

# 3. Healthcare-Associated Infection

The leading fungal pathogen causing healthcare-associated infection

# *Candida*

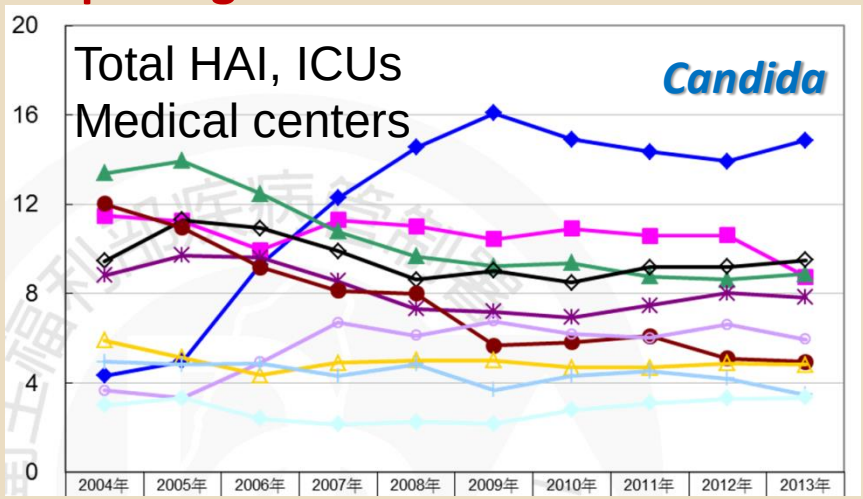
# The scope of the problem in Taiwan

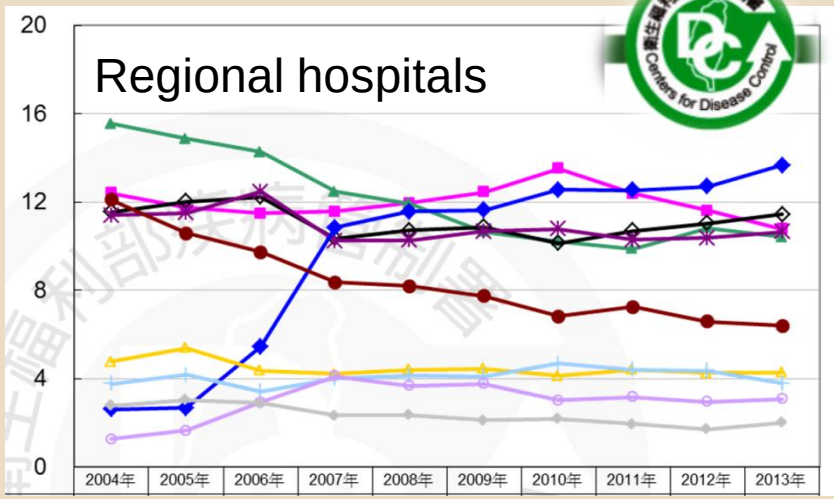
## *NTUH*

- *Candida* were the leading pathogens of healthcare-associated bloodstream infection (HABSI) since 1993 at NTUH.[1]
- Average annual change of *C. albicans* HABSI during 1981-2007 was 13.5% (8.7% -18.4%).[2]

## *Taiwan*

- *Candida* was the **2nd HABSI pathogen** since 2009/2008 and **1st urinary pathogen** since 2007.[3]

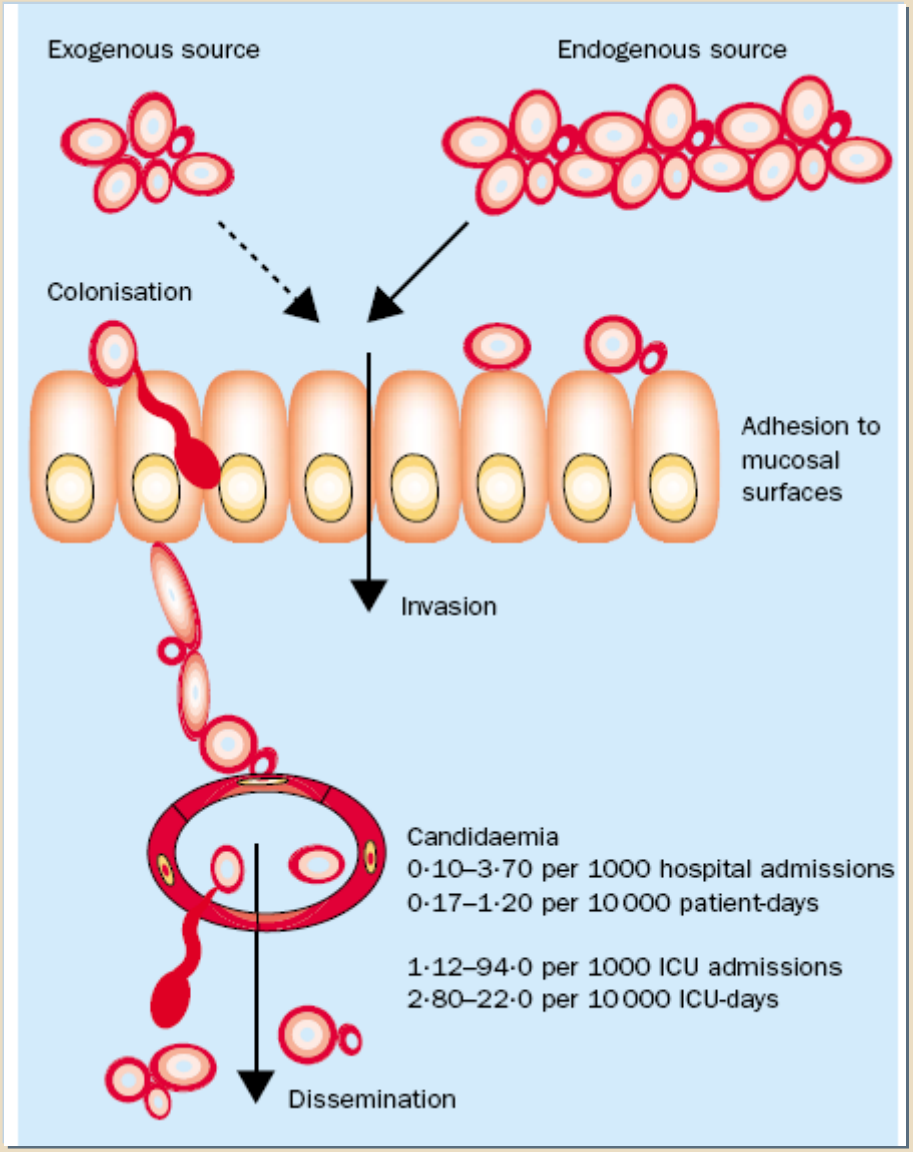



- Blood/total clinical isolates collected in TSARY was higher in 2010 (20%) than in 2006 (15%) and 2002 (14%).[4]

[1] Chen YC et al. Infect Control Hosp Epi 1997;18:369-75.
[2] Chuang YC et al. J Hosp Infect 2010;76:143
[3] TNIS data, CDC, Taiwan
[4] Yang YL et al. DMID 2013;76:182

# Pathophysiology of invasive candidiasis




**Endogenous:** The organisms are normal commensals of humans and are commonly found on skin, throughout the entire gastrointestinal tract, in expectorated sputum, in the female genital tract, and in the urine of patients with indwelling Foley catheters.

**Exogenous:** There is a relatively high incidence of carriage on the skin of health care workers.


Eggimann et al. Lancet Infect Dis 2003; 3: 685–702
Chen et al. J Formos Med Assoc 2001;100:791
Chen et al. J Clin Microbiol 2006;44:2172
Chen et al. Infect Genet Evol. 2009;9:912
Lin et al. J Clin Microbiol 2007;45:2452-9.
Huang et al. J Hosp Infect, 1998;39:47

# Incidence and species distribution of candidaemia in Asia: a laboratory-based surveillance study

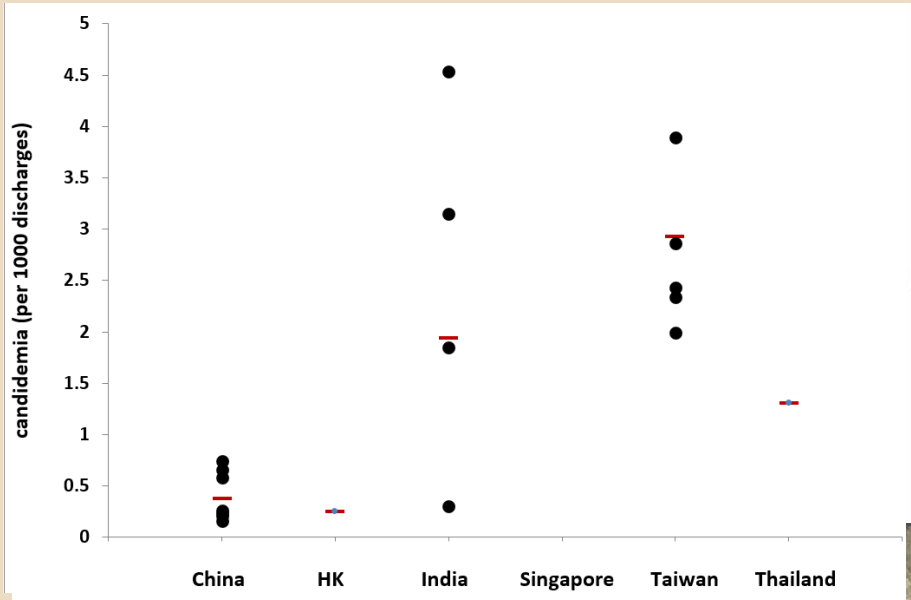
**B. H. Tan[1], A. Chakrabarti[2], R. Y. Li[3], A. K. Patel[4], S. P. Watcharananan[5], Z. Liu[6], A. Chindamporn[7], A. L. Tan[8], P.-L. Sun[9], U.-I. Wu[10] and Y.-C. Chen[11,12], on behalf of the Asia Fungal Working Group (AFWG)**

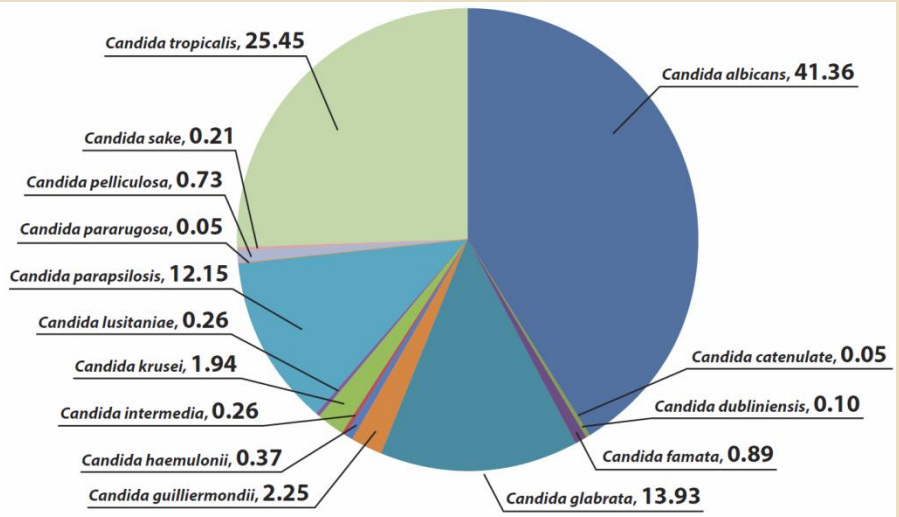
*1) Department of Infectious Diseases, Singapore General Hospital, Singapore, 2) Department of Medical Microbiology, Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh, India, 3) Department of Dermatology, Peking University First Hospital, Research Centre for Medical Mycology, Peking University, Beijing, China, 4) Department of Infectious Diseases, Sterling Hospital, Ahmedabad, India, 5 )Division of Infectious Disease, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand, 6 )Department of Infectious Diseases, Peking Union Medical College Hospital, Beijing, China, 7 ) Department of Microbiology, Faculty of Medicine, King Chulalongkorn Memorial Hospital Chulalongkorn University, Bangkok, Thailand, 8 )Department of Pathology, Singapore General Hospital, Singapore, 9 )Department of Dermatology, Mackay Memorial Hospital, 10 )Department of Medical Research, National Taiwan University Hospital, 11 )Department of Medicine, National Taiwan University Hospital and College of Medicine, Taipei and 12 )National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Miaoli County, Taiwan*

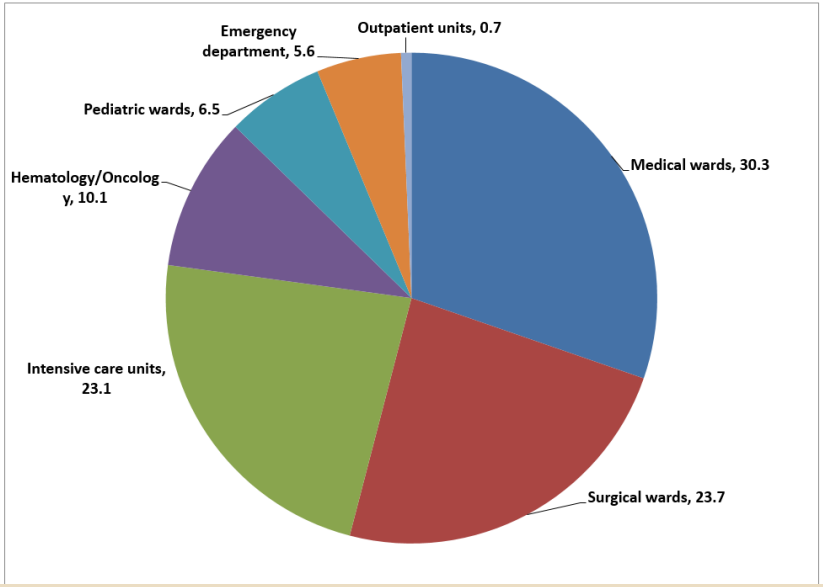
- The overall incidence was 1.22 episodes per 1,000 discharges or 0.15 episodes/1000 patient-days
- Varied among the hospitals (0.16–4.53) and countries ( 0.25–2.93).
- There was a moderate correlation between incidence of candidaemia and the ICU/total bed ratio ($R^2$=0.47), although ICUs contributed to only 23% of candidaemia cases.

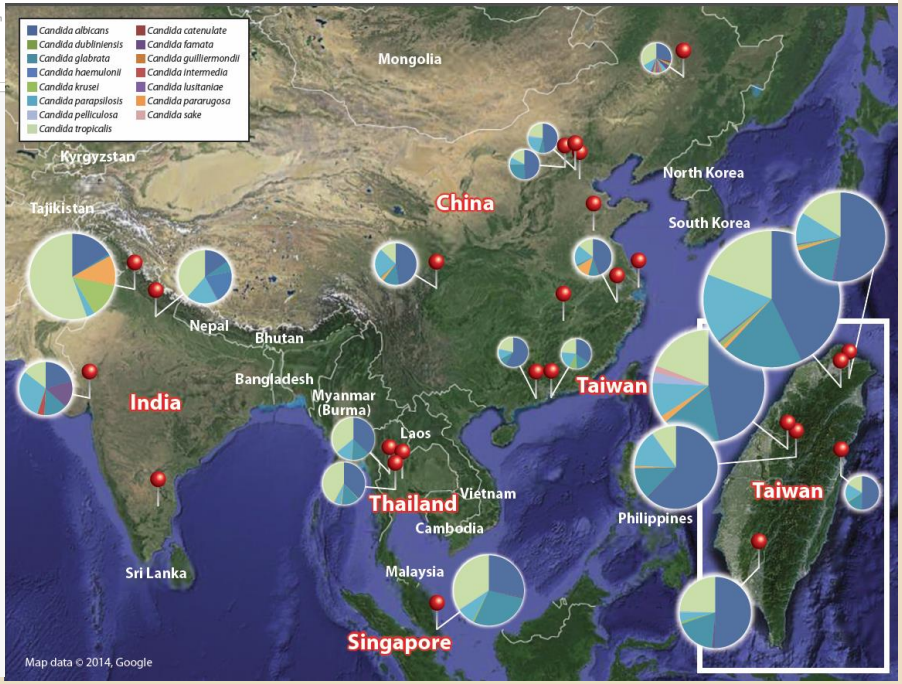


Clin Microbiol Infect 2015; 21: 946–953




Clin Microbiol Infect 2015; 21: 946–953

# Incidence of candidaemia by country/region

| Country or region | Setting or population | Study period | episodes | Incidence (range) | Incidence density (range) | Reference |
|---|---|---|---|---|---|---|
| **Hospital-based survey** | | | | | | |
| China | 9 hospitals | 2010–2011 | 310 | 0.38 per 1000 discharges (0.16–0.74) | 0.05 per 1000 patient-days (0.01–0.06) | Current study |
| Hong Kong | 1 hospitals | 2010–2011 | 30 | 0.25 per 1000 discharges | 0.07 per 1000 patient-days | Current study |
| India | 3 hospitals | 2010–2011 | 333 | 1.94 per 1000 discharges (0.30–4.53) | 1.24 per 1000 patient-days (0.30–1.77) | Current study |
| Singapore | 1 hospitals | 2010–2011 | 73 | NA | 0.15 per 1000 patient-days | Current study |
| Taiwan | 6 hospitals | 2010–2011 | 1104 | 2.93 per 1000 discharges (1.99–3.89) | 0.37 per 1000 patient-days (0.20–0.56) | Current study |
| Thailand | 3 hospitals | 2010–2011 | 130 | 1.31 per 1000 discharges | 0.17 per 1000 patient-days | Current study |
| Asia | 25 hospitals in 6 countries/ regions | 2010–2011 | 1601 | 1.22 per 1000 discharges (0.16–4.53) | 0.15 per 1000 patient-days (0.01–1.77) | Current study |
| Latin American | 21 tertiary care hospitals in 7 countries | 2008–2010 | 672 | 1.18 per 1000 admissions (0.21–2.98) | 0.23 per 1000 patient-days (0.06–0.39) | [4] |
| Italy | 34 hospitals | 2009 | 467 | 1.19 per 1000 admissions | | [5] |
| UK | A tertiary referral center. | 2005–2008 | 107 | | 0.109 per 1000 bed-days | [6] |
| **Intensive care units (ICUs)** | | | | | | |
| Asia | ICUs in 25 hospitals in 6 countries/regions | 2010–2011 | 370 | 11.7 per 1000 discharges | | Current study |
| India | 27 ICUs | 2011–2012 | 1,400 | 6.51 per 1000 ICU admission | | [7] |
| China | 67 adult ICUs | 2009–2011 | 306 | 3.2 per 1000 ICU admission | | [8] |
| Italy | 18 adult ICUs | 2007–2008 | 92 | 16.5 cases per 1000 admissions | | [9] |
| Germany | 682 ICUs | 2006–2011 | 523 | 0.24 per 1000 patients | 0.07 per 1000 patient-days | [10] |
| **Population-based survey** | | | | | | |
| Spain | Population survey (29 hospitals in five municipal areas) | 2010–2011 | 773 | 8.1 cases per 100 000 inhabitants 0.89 per 1000 admissions | 1.36 per 10 000 patient-days | [11] |
| USA | Population survey | 2008–2011 | 2675 | 13.3 per 100 000 person-years in Atlanta; 26.2 per 100 000 person-years in Baltimore | | [12] |
| Australia | Nationwide survey | 2000–2004 | 1095 | 1.81 per 100 000 population and 0.21 per 1000 separations | | [13] |
| Iceland | Nationwide survey | 2000–2011 | 208 | 5.7 per 100 000 population/year | | [14] |
| Finland | Nationwide survey | 2004–2007 | 603 | 2.86 per 100 000 population | | [15] |

Among rare *Candida* species, *C. pelliculosa*, also known as *Pichia anomala* or *Hansenula anomala*, is mainly found in plants, fruits and oil. Ten out of 14 episodes in this cohort were reported from a single hospital, clustered in the ICUs. In the preceding year, this hospital identified a monoclonal outbreak of *C. pelliculosa.*

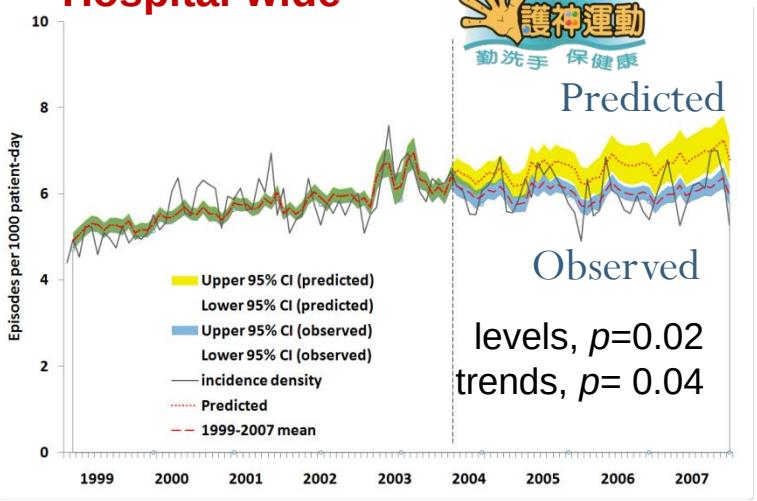
Clin Microbiol Infect 2015; 21: 946

J Microbiol Immunol Infect 2013;46:456

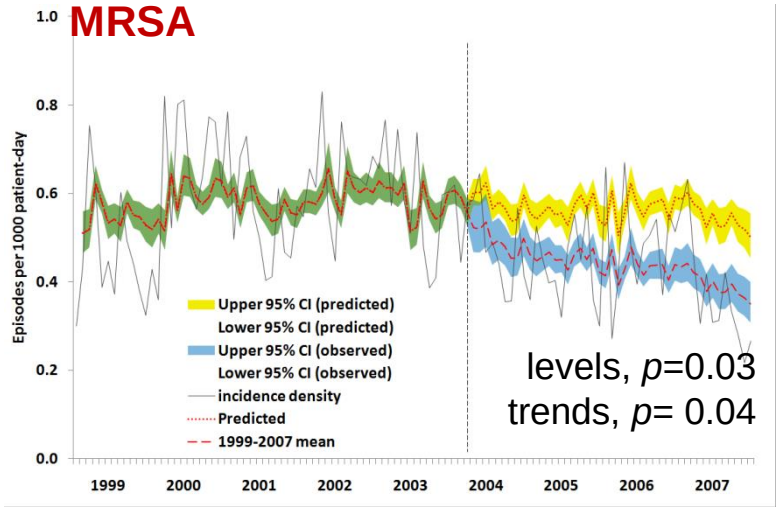
# Hand hygiene and healthcare-associated infection

## The disease severity score (Charlson comorbidity index) increased ($p$=0.002) in the intervention period. Nevertheless there was an 8.9% decrease in HAIs.

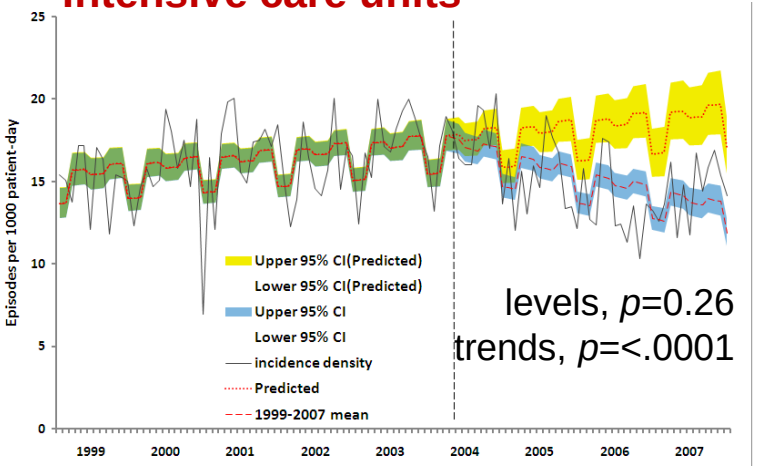
### Hospital-wide



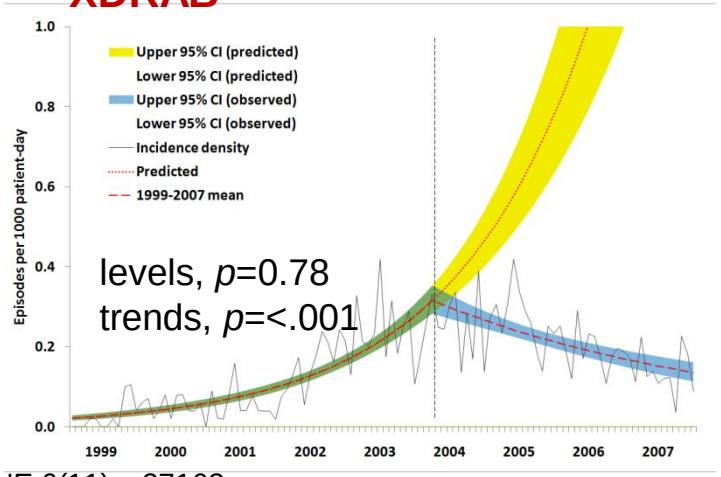

### MRSA




### Intensive care units




### XDRAB






YC Chen, et al PLoS ONE 6(11): e27163

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ORIGINAL ARTICLE

# Comparison of epidemiology and treatment outcome of patients with candidemia at a teaching hospital in Northern Taiwan, in 2002 and 2010

Pao-Yu Chen [a,b], Yu-Chung Chuang [a,b], Jann-Tay Wang [a,b], Wang-Huei Sheng [a,b], Chung-Jen Yu [a,c,d], Chen-Chen Chu [e], Po-Ren Hsueh [a,f], Shan-Chwen Chang [a,b,c], Yee-Chun Chen [a,b,c,*]

| | 2002 | 2010 |
|---|---|---|
| Incidence, per 1000 patients | 2.78 | 2.88 (p = 0.71) |
| Incidence density, per 1000 patient-days | 0.34 | 0.41 (p=0.04). |

**The incidence density of candidemia was high and increased in 2010 compared with 2002, which was at least in part due to the increase in patients at a higher risk of candidemia.**

# Risk factors associated with candidemia

## a hospital-based population study, NTUH, 2010

| Parameters | Univariate analysis | | | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|---|---|
| | Odds ratio | 95% confidence interval | | *p* value | Odds ratio | 95% confidence interval | | *p* value |
| | | Lower | Upper | | | Lower | Upper | |
| Age | | | | | | | | |
| 0–12 mo | 2.54 | 1.04 | 6.17 | 0.04 | 3.67 | 1.50 | 8.97 | 0.004 |
| 1–19 y | 1.08 | 0.54 | 2.14 | 0.82 | 1.07 | 0.54 | 2.13 | 0.85 |
| 20–44 y (as reference) | | | | | | | | |
| 45–64 y | 2.65 | 1.73 | 4.07 | <0.001 | 2.18 | 1.42 | 3.30 | <0.001 |
| ≥65 y | 3.70 | 2.43 | 5.64 | <0.001 | 2.64 | 1.72 | 4.06 | <0.001 |
| Sex, male | 1.48 | 1.17 | 1.88 | 0.001 | | | | |
| Charlson comorbidity index | | | | | | | | |
| 0–1 (as reference) | | | | | | | | |
| 2 | 2.57 | 1.68 | 3.92 | <0.001 | | | | |
| 3 | 3.94 | 2.49 | 6.21 | <0.001 | | | | |
| ≥4 | 6.62 | 4.63 | 9.47 | <0.001 | | | | |

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# Risk factors associated with candidemia

## a hospital-based population study

| Parameters | Univariate analysis | | | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|---|---|
| | Odds ratio | 95% confidence interval | | *p* value | Odds ratio | 95% confidence interval | | *p* value |
| | | Lower | Upper | | | Lower | Upper | |
| Underlying diseases/status | | | | | | | | |
| Congestive heart failure | 2.24 | 1.42 | 3.54 | 0.001 | | | | |
| Cerebrovascular diseases | 1.39 | 0.86 | 2.24 | 0.18 | | | | |
| Chronic pulmonary diseases | 2.27 | 1.52 | 3.41 | <0.001 | 1.90 | 1.25 | 2.89 | 0.003 |
| Connective tissue diseases | 1.12 | 0.55 | 2.26 | 0.76 | | | | |
| Moderate-to-severe liver diseases | 1.37 | 0.83 | 2.28 | 0.22 | | | | |
| Moderate-to-severe renal diseases | 8.76 | 6.70 | 11.46 | <0.001 | 8.08 | 6.11 | 10.67 | <0.001 |
| Diabetes mellitus without end organ damage | 1.46 | 1.08 | 1.98 | 0.01 | | | | |
| Diabetes mellitus with end organ damage | 0.95 | 0.35 | 2.55 | 0.92 | | | | |
| Any tumor | 1.16 | 0.91 | 1.48 | 0.23 | | | | |
| Lymphoma | 3.33 | 2.11 | 5.25 | <0.001 | 3.98 | 2.49 | 6.35 | <0.001 |
| Leukemia | 3.68 | 2.38 | 5.71 | <0.001 | 4.58 | 2.90 | 7.23 | <0.001 |
| Gastrointestinal malignancy | 3.93 | 2.83 | 5.46 | <0.001 | 2.80 | 1.93 | 4.05 | <0.001 |
| Metastatic solid tumor | 2.51 | 1.93 | 3.26 | <0.001 | 2.32 | 1.72 | 3.14 | <0.001 |
| Neutropenia | 3.06 | 1.75 | 5.35 | <0.001 | | | | |
| Acquired immunodeficiency syndrome | 2.44 | 0.78 | 7.66 | 0.12 | | | | |
| Solid organ transplant (kidney, liver, heart, pancreas) | 1.70 | 0.63 | 4.57 | 0.29 | | | | |

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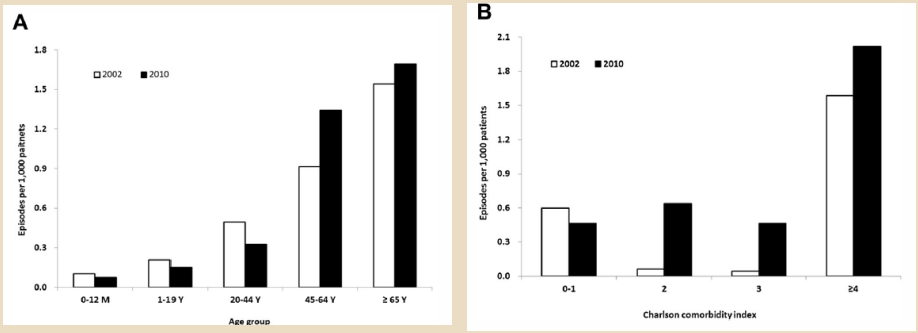
# Disease-specific incidence of candidemia




| Parameters | 2002 ($n$ = 218) | 2010 ($n$ = 286) | $p$ value |
|---|---|---|---|
| Congestive heart failure | 10 (7.91) | 20 (7.71) | >0.99 |
| Cerebrovascular diseases | 22 (6.81) | 18 (4.89) | 0.37 |
| Chronic pulmonary diseases | 22 (8.37) | 26 (7.71) | 0.89 |
| Connective tissue diseases | 2 (2.42) | 8 (4.00) | 0.81 |
| Moderate-to-severe liver diseases | 20 (4.91) | 16 (4.85) | >0.99 |
| Moderate-to-severe renal diseases | 54 (15.13) | 73 (23.83) | 0.01 |
| Diabetes mellitus without end organ damage | 21 (3.86) | 52 (4.94) | 0.41 |
| Diabetes mellitus with end organ damage | 3 (3.27) | 4 (3.40) | >0.99 |
| Any tumor | 52 (3.90) | 104 (3.95) | >0.99 |
| Lymphoma | 11 (12.72) | 20 (16.99) | 0.56 |
| Leukemia | 17 (14.33) | 22 (12.37) | 0.76 |
| Gastrointestinal malignancy | 36 (28.80) | 42 (12.44) | <0.001 |
| Metastatic solid tumor | 53 (11.91) | 76 (7.53) | 0.01 |
| Neutropenia | 11 (11.54) | 13 (8.67) | >0.99 |
| Acquired immunodeficiency syndrome | 3 (12.10) | 3 (10.56) | 0.89 |
| Solid organ transplantation (kidney, liver, heart, pancreas) | 2 (5.10) | 4 (6.04) | >0.99 |
| Hematopoietic stem cell transplantation | 0 (0.00) | 0 (0.00) | — |

Per 1000 patients

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# Characteristics of patients hospitalized at NTUH

| Parameters | 2002 | 2010 | *p* value |
|---|---|---|---|
| Number of acute care beds | 2200 | 2300 | — |
| Total number of admissions | 66,763 | 79,710 | — |
| Total number of patient-days | 632,318 | 691,692 | — |
| Age, y | 47.3 ± 23.6 | 51.2 ± 22.9 | <0.001 |
| Sex, male (%) | 34,514 (54.58) | 39,669 (57.35) | <0.001 |
| Charlson comorbidity index | 2.10 ± 3.45 | 3.18 ± 4.33 | <0.001 |
| Underlying disease/status, **N (0/00)** | | | |
| Congestive heart failure | 1264 (18.93) | 2595 (32.56) | <0.001 |
| Cerebrovascular diseases | 3230 (48.38) | 3682 (46.19) | 0.04 |
| Chronic pulmonary diseases | 2629 (39.38) | 3372 (42.30) | 0.005 |
| Connective tissue diseases | 828 (12.40) | 2002 (25.12) | <0.001 |
| Moderate-to-severe liver diseases | 4076 (61.05) | 3302 (41.43) | <0.001 |
| Moderate-to-severe renal diseases | 3568 (53.44) | 3063 (38.43) | <0.001 |
| Diabetes mellitus without end organ damage | 5447 (81.59) | 10,530 (132.10) | <0.001 |
| Diabetes mellitus with end organ damage | 918 (13.75) | 1177 (14.77) | 0.10 |
| Any tumor[a] | 13,330 (199.66) | 26,312 (330.10) | <0.001 |
| Lymphoma | 865 (12.96) | 1776 (22.28) | <0.001 |
| Leukemia | 1186 (17.76) | 1779 (22.32) | <0.001 |
| Gastrointestinal malignancy[b] | 1250 (18.72) | 3377 (42.37) | <0.001 |
| Metastatic solid tumor | 4451 (66.67) | 10,090 (126.58) | <0.001 |
| Acquired immunodeficiency syndrome | 260 (3.89) | 346 (4.34) | 0.19 |
| Neutropenia | 909 (13.62) | 1231 (15.44) | 0.004 |
| Solid organ transplantation (kidney, liver, heart, pancreas) | 392 (5.87) | 662 (8.31) | <0.001 |
| Hematopoietic stem cell transplantation | 29 (0.43) | 106 (1.00) | <0.001 |
| Incidence density of candidemia (per 1000 patient-days) | 218 (0.34) | 286 (0.41) | 0.04 |

[a] Any tumor is defined as any solid malignancy excluding gastrointestinal malignancy, metastatic malignancy, leukemia and lymphoma.
[b] Gastrointestinal malignancy indicates malignancies involving any part of the following organs: esophagus, stomach, small or large intestines, and rectum.

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# Conclusion

# Conclusion

- BEWARE!
  - Alertness of primary care physicians to suspect fungal infection and collect specimens for microbiological confirmation
  - Alertness of microbiologists to conduct good laboratory practice to prevent lab contamination, further species identification, identify unusual increase in cases
- Surveillance and reporting system: national or regional
  - Importance of local epidemiology (incidence and local clonality)
- Response system: to clarify the diagnosis, further testing to support further clinical management, and outbreak investigation
- Source control

**Concern: Are we capable to detect, identify, confirm and control such events?**