

Lecture – UZ Leuven – 09/12/2025

Serious fungal infections in the Democratic Republic of Congo

The country's potential to bear a heavy burden, and the specific case of cryptococcosis

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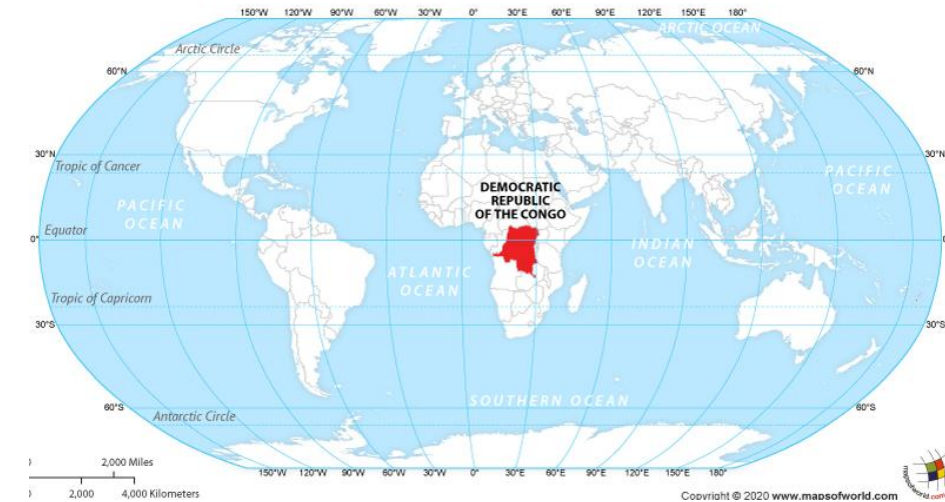
Outline

01. Why are we convinced that the DRC has the potential to bear a heavy burden of invasive fungal infections?

- Global burden of fungal infections (numbers and risk factors)
- Current epidemiology of conditions that could expose people to fungal infections in the DRC (HIV, TB, bronchial asthma, cancers and chemotherapy, etc.)

02. What about cryptococcosis in DRC?

- Cryptococcosis in Retrospect
- What we already know about cryptococcosis today?
- Perspective on research, screening of at-risk patients, and treatment



01. Why are we convinced that the DRC has the potential to bear a heavy burden of invasive fungal infections?

Global burden of fungal infections (numbers and risk factors) (1)

- \pm **6.5 million** patients develop life-threatening fungal infections annually worldwide.
- More than half (**3.75 million**) of them unfortunately do not survive.
- These deaths are mainly due to the following fungal diseases:

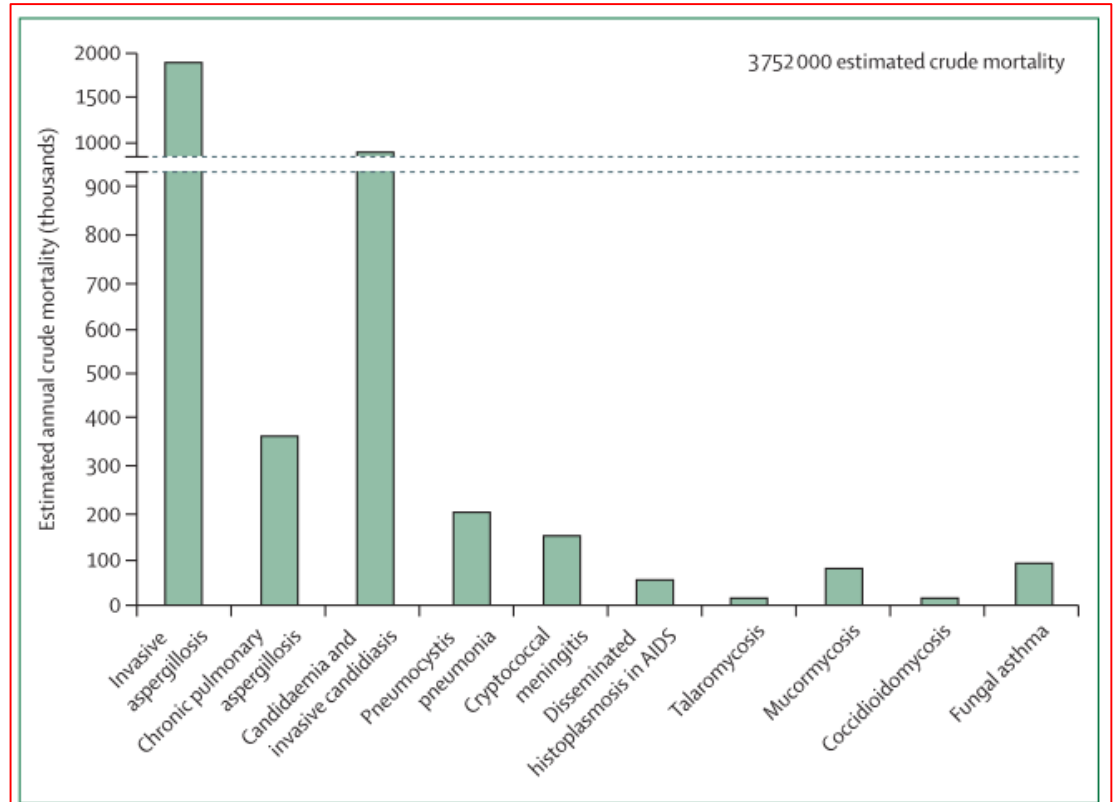
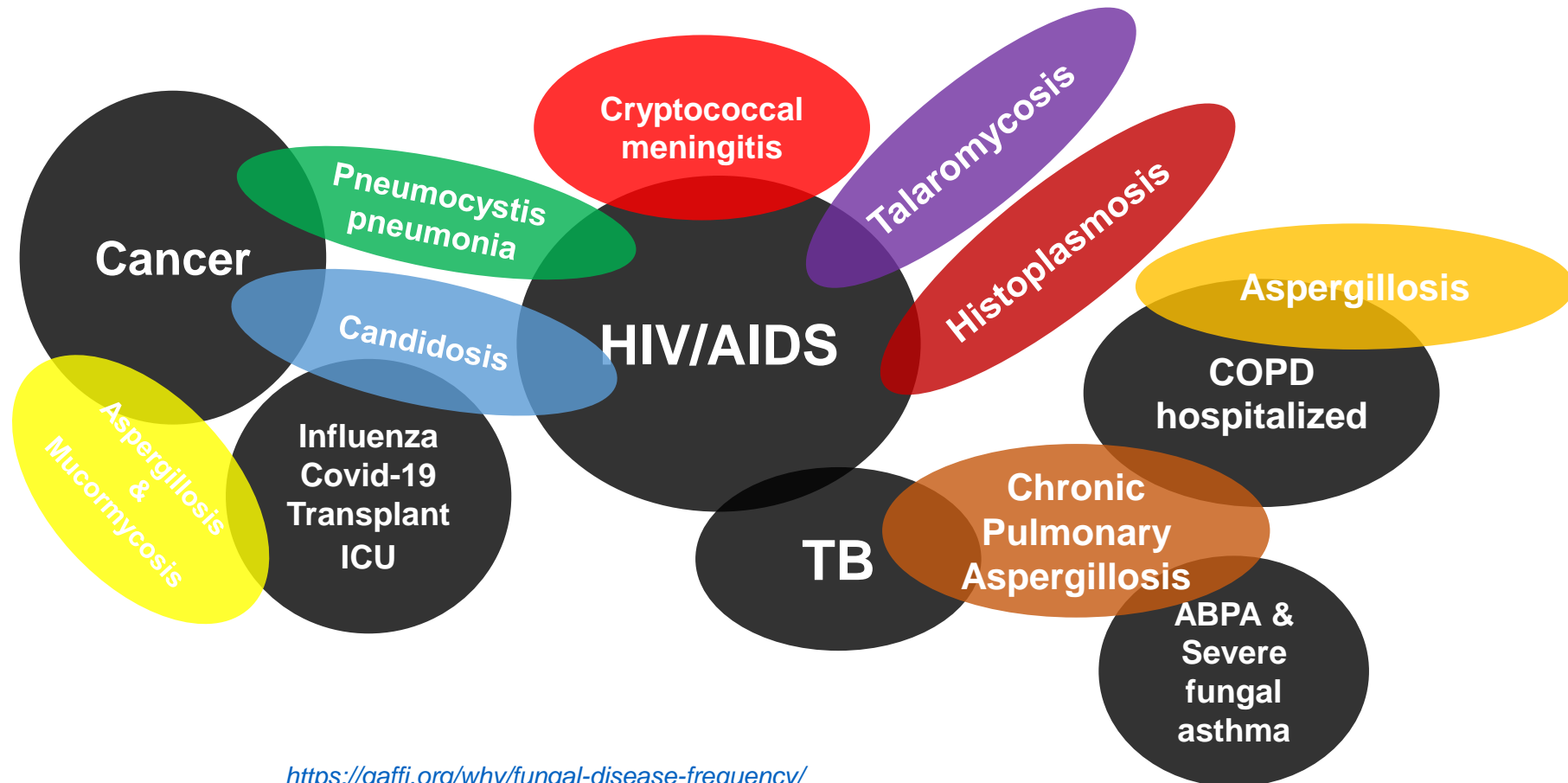


Figure 2: Estimated crude mortality of severe fungal disease, worldwide

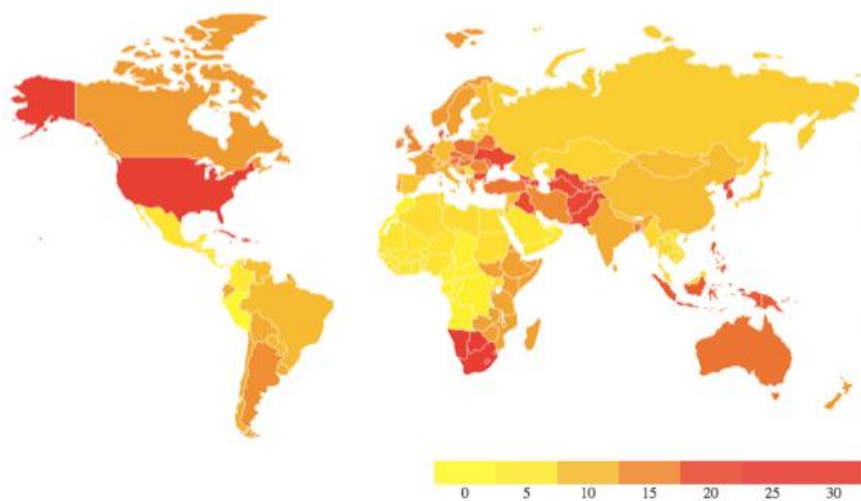
Global burden of fungal infections (numbers and risk factors) (2)

- Fungal infections mainly develop in patients with specific risk factors (= immunocompromised patients).
- Sometimes in immunocompetent patients.

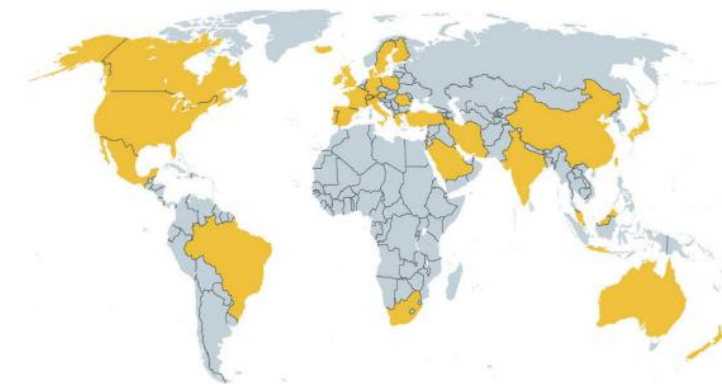


Global burden of fungal infections (numbers and risk factors) (3)

- **Significant gaps** in the representation of global data on fungal infections.
- Many countries around the world lack basic data, particularly **certain African countries** such as **the DRC**.
- Making it difficult to accurately **estimate the global burden of fungal infections** → difficult to implement **effective measures on a global scale**.
- Case of glaring disparity in global data on **aspergillosis syndromes**:



Incidence of invasive aspergillosis
In COPD

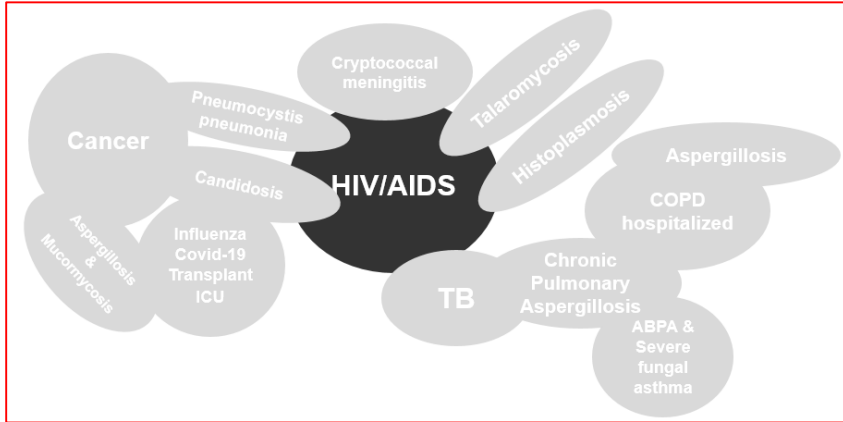


Global burden of fungal infections (numbers and risk factors) (4)

- There is therefore a need to supplement global data in order to improve our overall understanding of the distribution, associated risk factors, epidemiology of pathogens, and characteristics of fungal infections in regions not yet covered.
- Which is what Gatti has been doing for many years around the world, in addition to his other missions.



Current epidemiology of conditions that could expose people to fungal infections in the DRC (1)



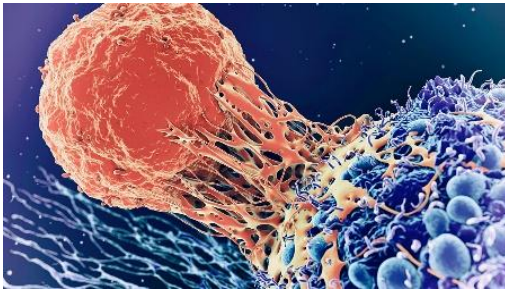
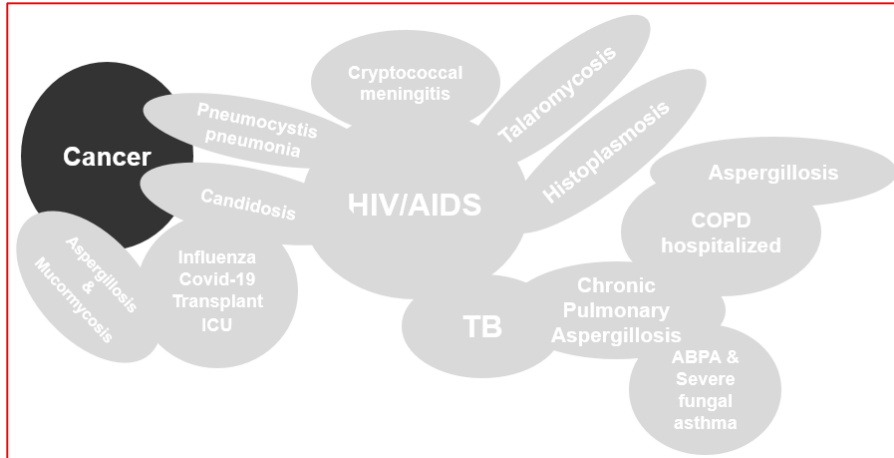
 **HIV infection**



2024 UNAIDS statistics for the DRC

- **610,000** HIV patients
- **77% (470,000 HIV patients)** of them are aware of their status
- \approx one-third (**29%**) of HIV patients don't have access to antiretroviral treatment
- \approx **30-60%** of all these patients would have advanced HIV infection → **highly exposed to opportunistic infections, fungal infections +++**

Current epidemiology of conditions that could expose people to fungal infections in the DRC (2)

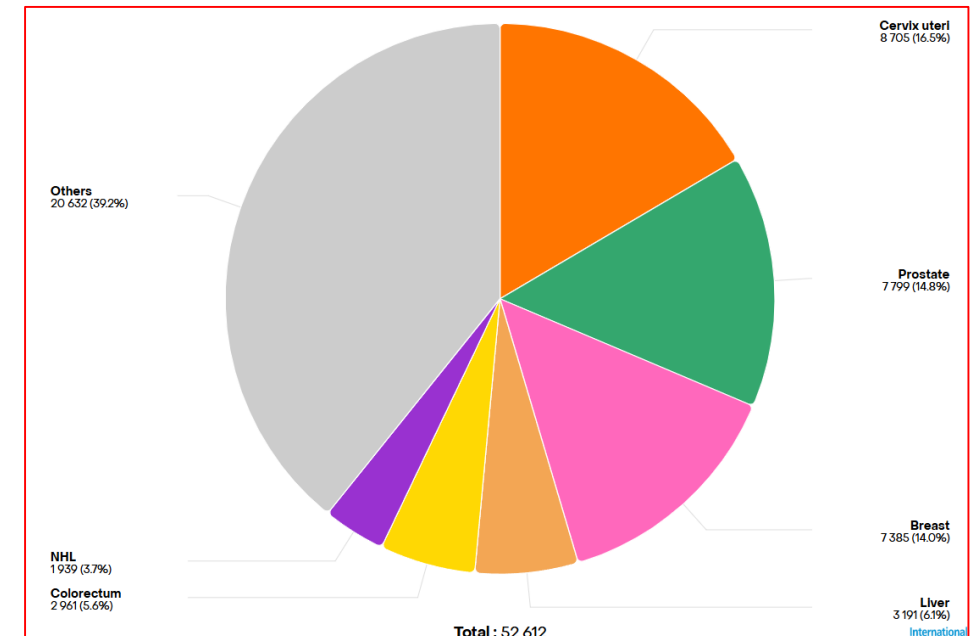
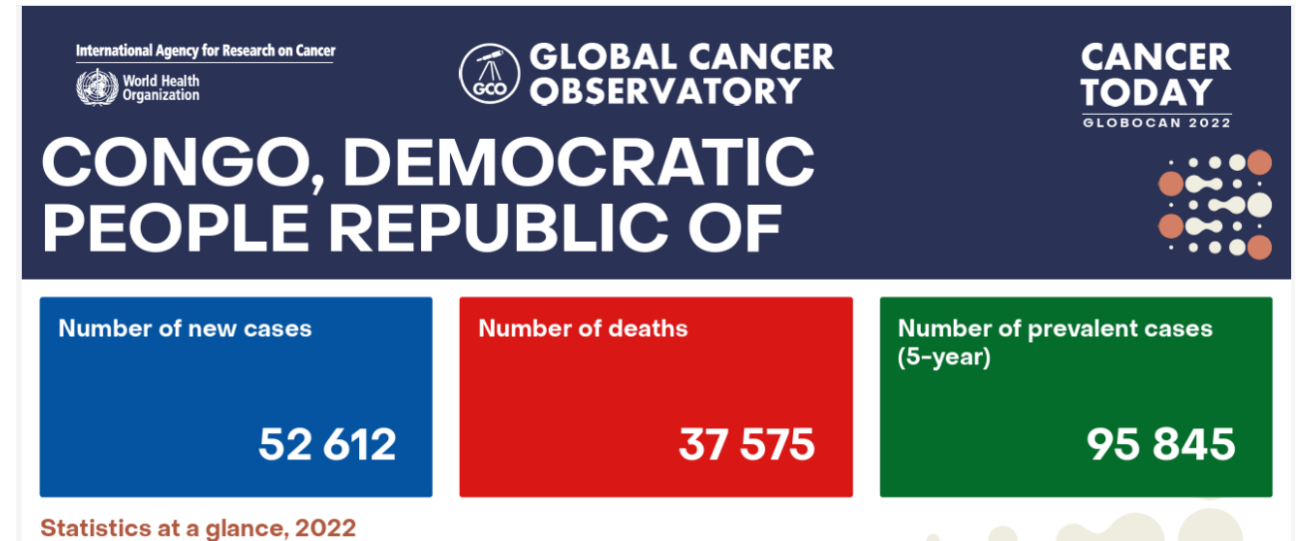


Cancer

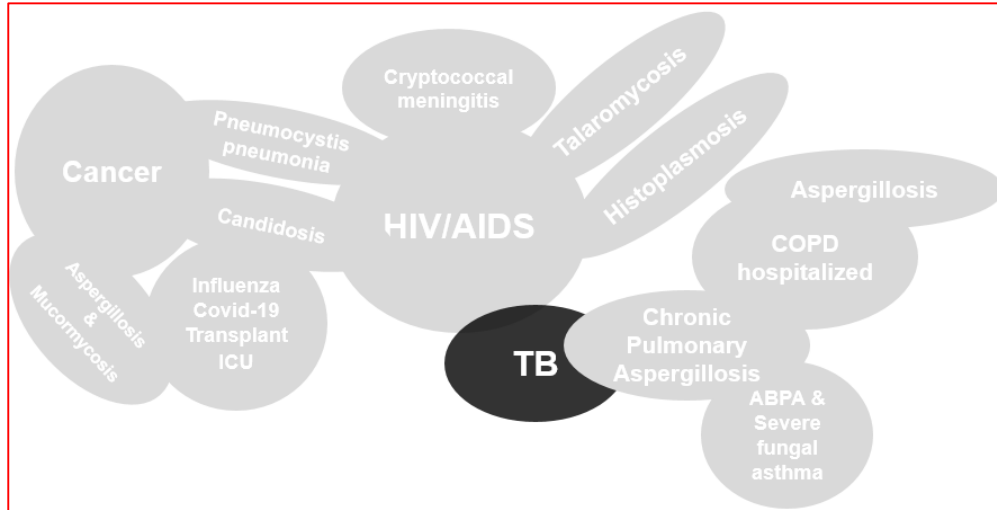
Organ transplantation

- Not yet operational in the DRC, awaiting approval of the relevant law by the National Assembly

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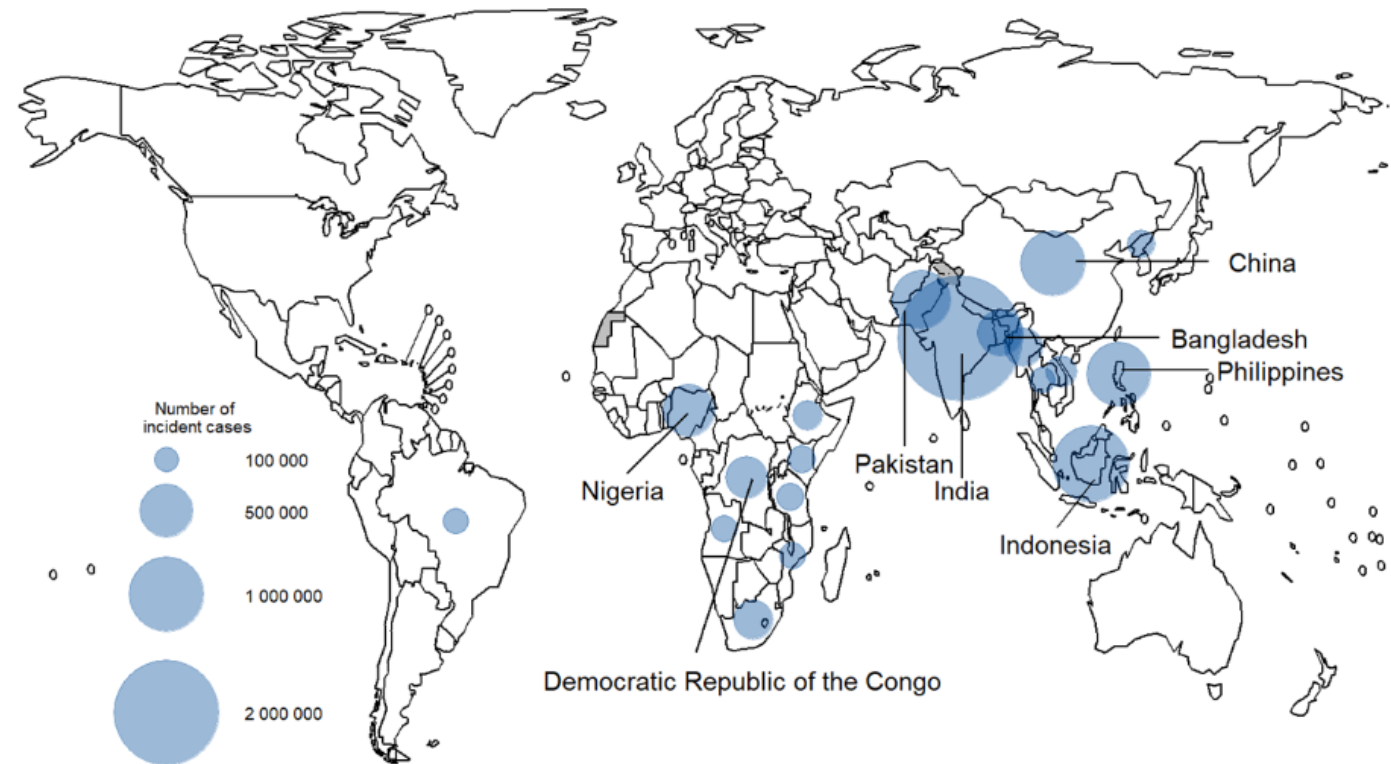


Current epidemiology of conditions that could expose people to fungal infections in the DRC (3)

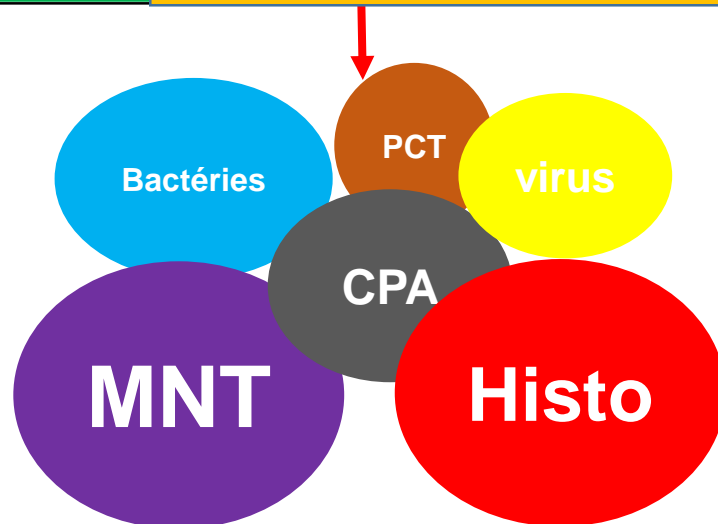
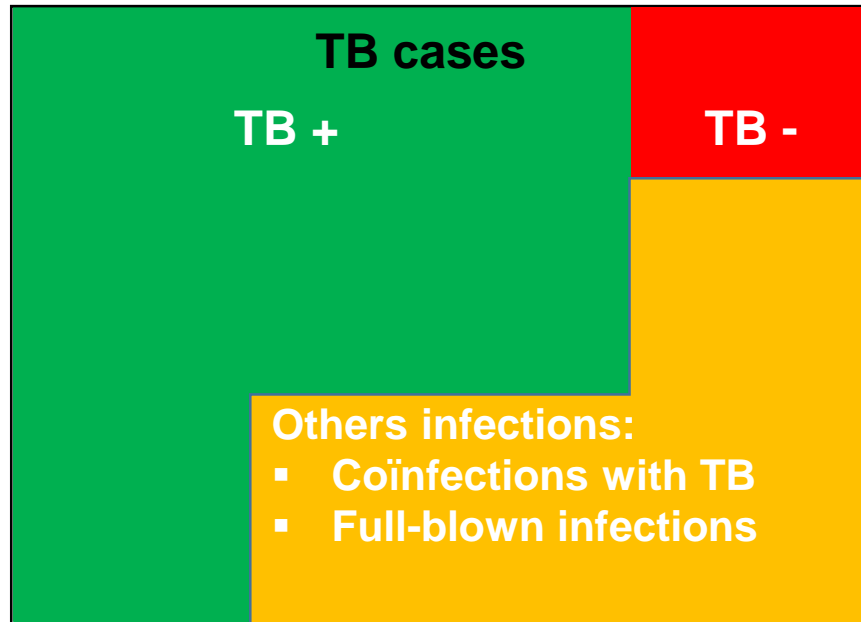


- The DRC is among the 30 countries that bear 87% of the global TB burden
- According to WHO estimates, **270,000 people** fell ill with TB in 2018
- Incidence : **316/100.000 habitants**

Tuberculosis (TB)



Current epidemiology of conditions that could expose people to fungal infections in the DRC (4)



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Revue d'Épidémiologie
et de Santé Publique
Epidemiology and Public Health

Revue d'Épidémiologie et de Santé Publique 63 (2015) 387–393

Article original

Issues thérapeutiques du traitement antituberculeux dans le contexte de la
co-infection VIH-tuberculose : cohorte du centre de Kabinda à Kinshasa,
République démocratique du Congo

*Therapeutic outcomes of anti-tuberculosis treatment in the context of HIV-tuberculosis
co-infection: Cohort of Kabinda Center in Kinshasa,
Democratic Republic of Congo*

P.Z. Akilimali *, J.M.K. Tshilumbu, A.K. Mavila, D.K. Kaba

École de santé publique, université de Kinshasa, PB 11850, Kinshasa, République démocratique du Congo

Reçu le 10 mai 2014 ; accepté le 11 septembre 2015

Disponible sur Internet le 5 novembre 2015

Abstract

Background. – The study aimed to determine the clinical forms of tuberculosis and therapeutic outcome of anti-tuberculosis treatment in the context of HIV-tuberculosis co-infection.

Methods. – A retrospective cohort of 120 HIV-positive patients with tuberculosis and 297 HIV-negative patients with tuberculosis attending the Kabinda Center was followed from 2010 to June, 30th 2013. The logistic regression model identified the determinants of a defavorable outcome after initiation of tuberculostatics.

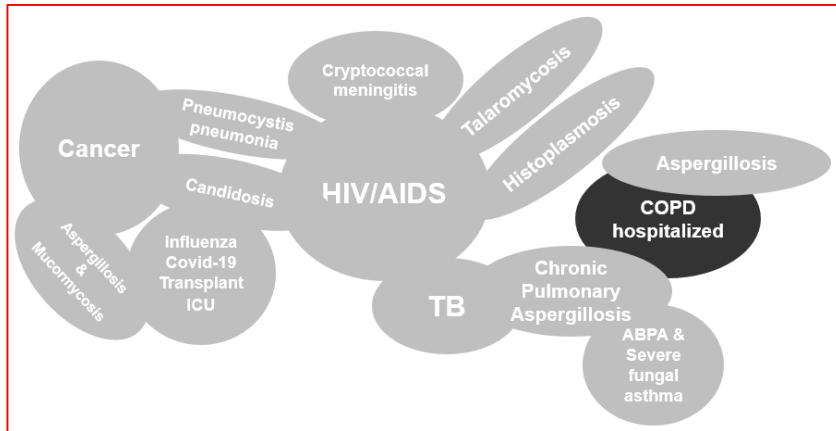
Results. – The proportion of female patients was higher in the co-infected group compared with the non-co-infected group (60.8% versus 42.7%, $P < 0.001$). HIV-seropositive patients had more forms of pulmonary smear-negative (39.2% versus 25.3%, $P < 0.002$) and extra-pulmonary (38% versus 35%, $P < 0.002$) tuberculosis than HIV-negative patients. HIV-positive serology (OR: 3.13, 95%CI: 1.72–5.69) and age of patients more than 41 years (OR: 3.15, 95%CI: 1.36–7.29) were associated with an unfavorable outcome.

Conclusion. – This study highlights the usefulness of a systematically determining immunological status in co-infected patients and a timely and systematic ARV treatment, together with early diagnosis of tuberculosis. It also emphasizes the importance of adherence to support measures in order to improve tuberculosis treatment outcomes in co-infected patients.

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42.7%, $P < 0.001$). HIV-seropositive patients had more forms of pulmonary smear-negative (39.2% versus 25.3%, $P < 0.002$) and extra-pulmonary (38% versus 35%, $P < 0.002$) tuberculosis than HIV-negative patients. HIV-positive serology (OR: 3.13, 95%CI: 1.72–5.69) and age of

Current epidemiology of conditions that could expose people to fungal infections in the DRC (5)



Chronic obstructive pulmonary disease (COPD)

Fréquence, Phénotypes, et Déterminants de la Bronchopneumopathie chronique obstructive (BPCO) aux Cliniques Universitaires de Kinshasa

Chronic obstructive pulmonary disease (COPD): Frequency, Phenotypes and Determinants at the Kinshasa University Hospital

Tshiasuma PM¹, Mbutiwi F², Tete OB²,
Kayembe NJM².

Tableau 1 : Distribution des pathologies respiratoires diagnostiquées chez les patients

| Pathologies | n=627 | % |
|--|------------|-------------|
| Tuberculose pulmonaire | 198 | 31,6 |
| Pneumonies et broncho-pneumonies non tuberculeuses | 185 | 29,5 |
| BPCO | 138 | 22,0 |
| Asthme bronchique | 66 | 10,5 |
| Pleurésies | 21 | 3,4 |
| Tumeurs broncho-pulmonaires | 16 | 2,6 |
| Bronchite aigue | 14 | 2,2 |
| Bronchectasies | 13 | 2,1 |
| PID | 9 | 1,4 |
| PHS | 4 | 0,6 |
| Embolie pulmonaire | 3 | 0,5 |
| Abcès pulmonaire | 2 | 0,3 |
| Mésothéliome | 1 | 0,2 |

Tableau 3 : Sévérité et modalités de prise en charge de la BPCO

| | N=138 | % |
|------------------------------|-----------|-------------|
| Degré de sévérité de la BPCO | | |
| GOLD 1 | 4 | 2,9 |
| GOLD 2 | 35 | 25,4 |
| GOLD 3 | 74 | 53,6 |
| GOLD 4 | 25 | 18,1 |
| Modalités thérapeutiques | | |
| Beta-2 mimétiques | 128 | 92,8 |
| Corticoïdes inhalés | 92 | 66,7 |
| Anticholinergiques | 40 | 29,0 |
| Antibiotiques | 4 | 2,9 |
| Oxygénothérapie | 8 | 5,8 |

Current epidemiology of conditions that could expose people to fungal infections in the DRC (6)



Annales Africaines de Médecine
Article original

Survie et prédicteurs de la mortalité des patients admis au Service de Réanimation polyvalente des Cliniques Universitaires de Kinshasa

Survival and predictors of mortality in Patients Admitted to the Multipurpose Intensive Care Unit of the University Hospital of Kinshasa

Christian Nantulu¹, Jean-Robert Makulo²,
†François Bompeka Lepira², Rigbo Shamamba¹,
Yannick Mayamba Nlandu², Eric Bibonge
Amisi¹, Adolphe Manzanza Kilembé¹

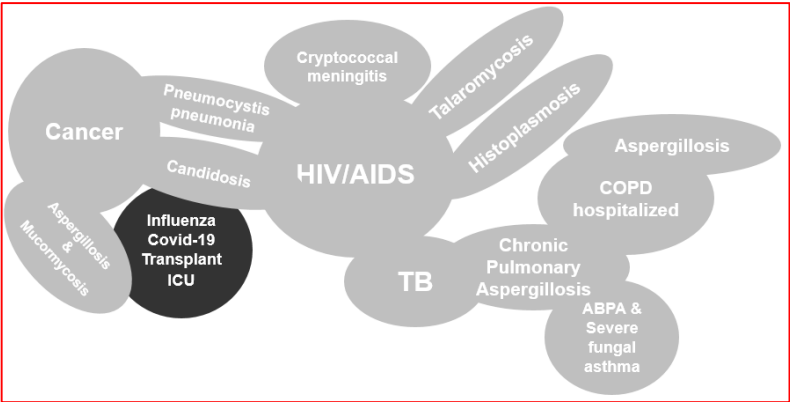
Correspondance

Jean-Robert Makulo
Courriel : jrmakulo2016@gmail.com

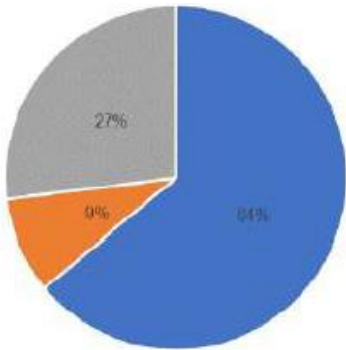
Résumé

Contexte et objectif. La réduction de la mortalité est une préoccupation majeure en réanimation. Notre objectif était de

Intensive care unit



- 320 patients hospitalized in 2 years (2016-2017)
- Overall survival rate of 18% on the 28th day of hospitalization



■ Pathologies médicales ■ Pathologies traumatiques ■ Pathologies chirurgicales

Tableau 2. Répartition des patients selon les motifs de transfert

| Motifs d'admission en Réanimation | n = 320 |
|-------------------------------------|-----------|
| AVC en phase aiguë, n (%) | 73 (22,8) |
| Surveillance post opératoire, n (%) | 69 (21,6) |
| Détresse respiratoire, n (%) | 37 (11,6) |
| Polytraumatisme, n (%) | 27 (8,4) |
| Sepsis, n (%) | 25 (7,8) |
| Coma métabolique, n (%) | 22 (6,9) |
| Etat de choc, n (%) | 19 (5,9) |
| Tétanos, n (%) | 10 (3,1) |
| Embolie pulmonaire, n (%) | 9 (2,8) |
| OAP, n (%) | 8 (2,5) |
| Etat de mal épileptique, n (%) | 5 (1,6) |
| Eclampsie, n (%) | 5 (1,6) |
| Insuffisance cardiaque, n (%) | 2 (0,6) |
| Neuropaludisme, n (%) | 2 (0,6) |
| Autres, n (%) | 7 (2,1) |

02. What about cryptococcosis in DRC?

What is cryptococcosis?

- Fungal infection due to ***Cryptococcus neoformans*/C. *gattii* species complex**
- Neuromeningeal form +++
- Epidemiology varies according to the immune status of patients

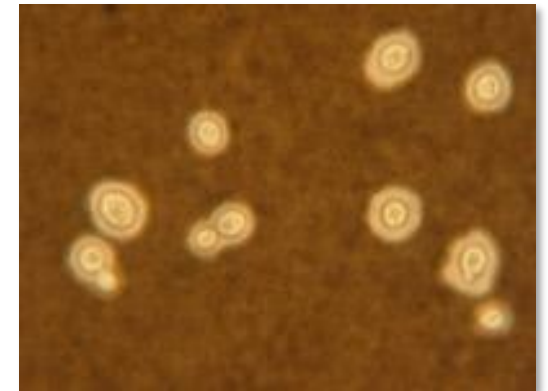


In HIV patients

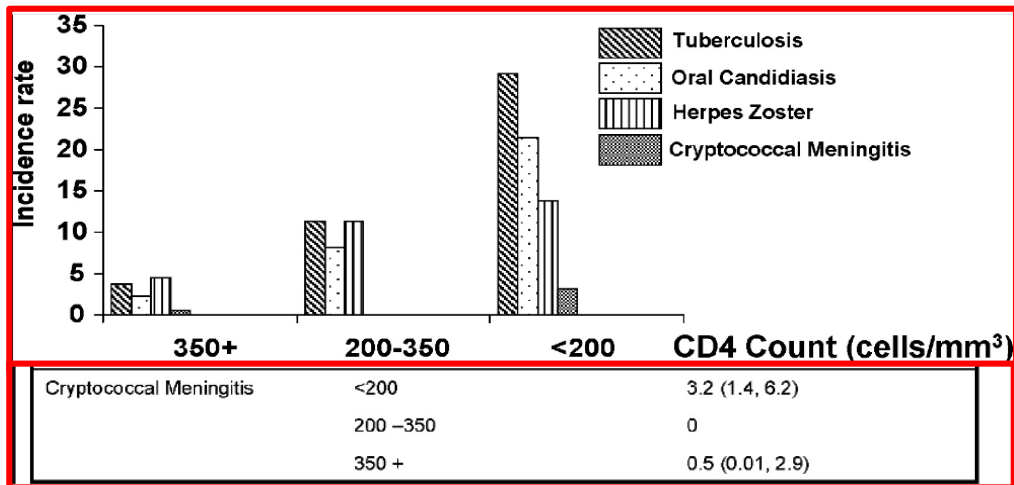
- Represents the **majority of global cryptococcosis cases**
- ***Cryptococcus neoformans* +++**
- **112,000 deaths** related to cryptococcal meningitis each year
- **≈ 19%** of all HIV deaths
- Sub-Saharan Africa & Asia > **2/3**

In non-HIV patients

- Developed countries +++
 - ***Cryptococcus gattii* +++**
- USA: **44-45% of cases among non-HIV individuals**
- In Europe: **23% in non-HIV**
- In sub-Saharan Africa: **9% among non-HIV individuals**



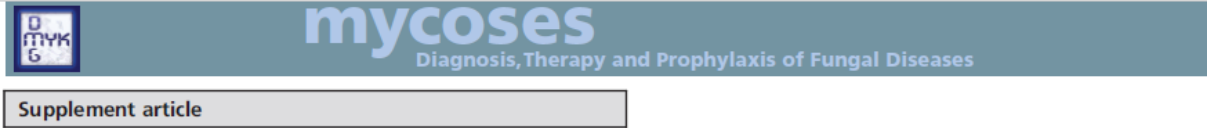
Predisposing factors



| Common risk factors | Rare primary immunodeficiencies |
|---|--|
| <ul style="list-style-type: none"> HIV +++ Solid organ transplant recipient Other immunosuppressive conditions: <ul style="list-style-type: none"> Malignant blood disorders Cirrhosis Rheumatoid arthritis Sarcoidosis Immunosuppressive drugs Idiopathic CD4 lymphopenia | <ul style="list-style-type: none"> Anti-cytokine antibodies (IFNγ, GM-CSF) X-linked hyper-IgM syndrome + CD40 ligand gene mutation Innate immune disorders ... |

Determining the patient's immunocompetent status will therefore depend on the laboratory's capabilities and medical guidance.

Cryptococcosis in Belgium



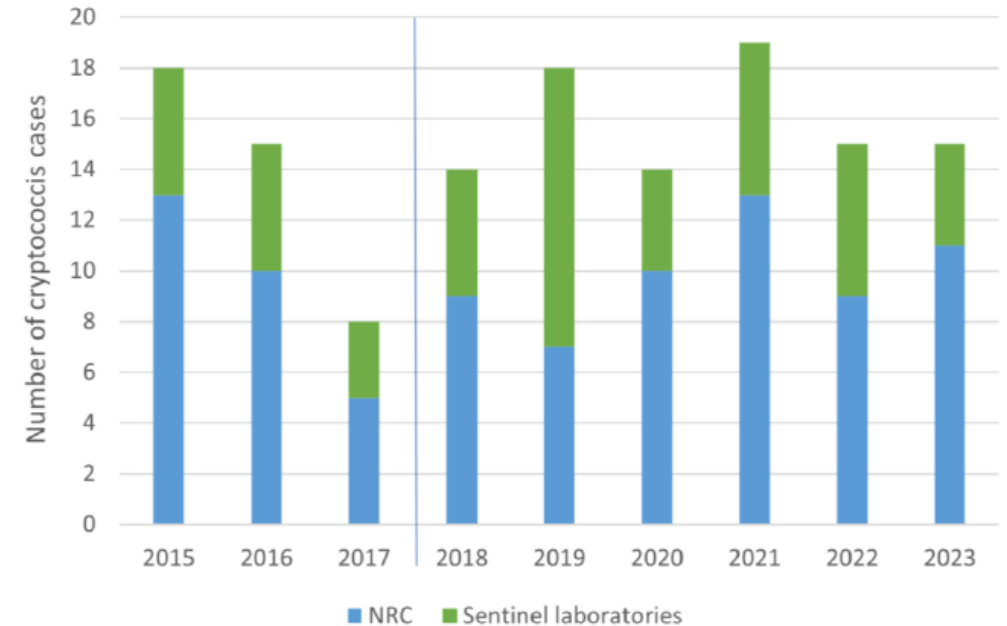
Burden of serious fungal infections in Belgium

Katrien Lagrou,^{1,2} Johan Maertens,¹ Ellen Van Even² and David W. Denning³

¹Department of Microbiology and Immunology, Catholic University Leuven, Leuven, Belgium, ²Department of Laboratory Medicine, National Reference Center for Mycosis, University Hospitals Leuven, Leuven, Belgium and ³National Aspergillus Centre, University Hospital of South Manchester, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK

- **2005 - 2014:** 3 to 12 isolats send to the NCR
- Patient profile : ???
- Incidence : 0.09 cases/100,000 inhabitants (year ?); 0.13/100,000 (**2016**); 0.07/100,000 (**2017**).

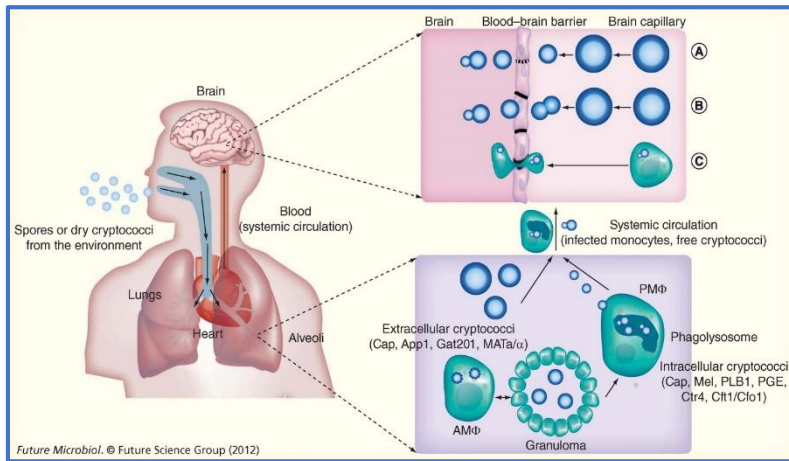
Annual case trends



Patient risk factors

- Solid organ transfert: 11/37
- **HIV infection: 6/37 (16.2%)**
- Malignancy: 6/37
- Another pathology: 6/37
- Diabetes: 2/37

Clinical manifestations



4 possible scenarios:

- Complete elimination of the fungus by the immune response
- Asymptomatic infection → latency with possibility of reactivation
- Pulmonary disease
- Dissemination to other organs (brain +++).

Cryptococcal meningitis

Subacute/chronic presentation

Symptoms/signs

- Headache (80-92%)
- Meningeal signs (50-80%)
- Nausea/vomiting (40-8%)
- Fever (36-67%)
- ...



Other manifestations:

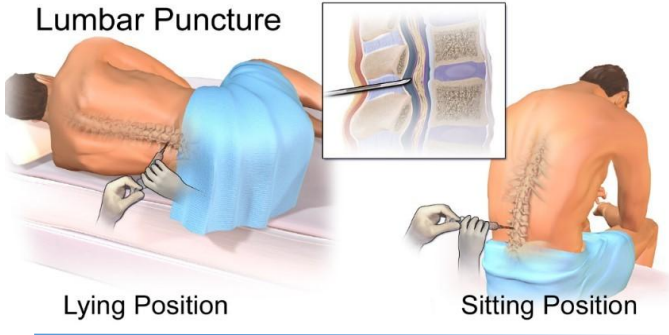
▪ Skin infections



- Ocular infections
- Urinary and prostatic infections
- Osteoarticular infections
- Cryptococcal lymphadenitis

Management – diagnosis

Meningeal cryptococcosis:



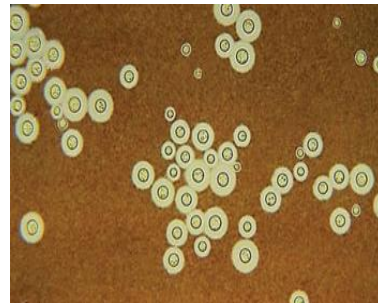
CSF Analysis

- Opening pressure >>>
- Appearance: clear (**rock water +++**)
- Cell count: 10-100/ μ L (lymphocytes ou mixed)
- High protein level > 2g/L
- Low glucose level < 0,5 g/L

Normal CSF: +++

Samples

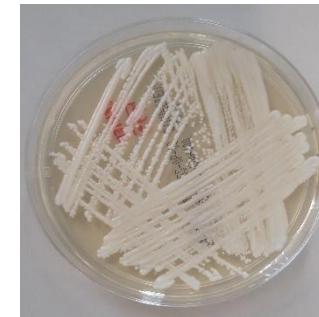
- CSF
- Blood
- Biopsy
- BAL fluid
- Urine ...



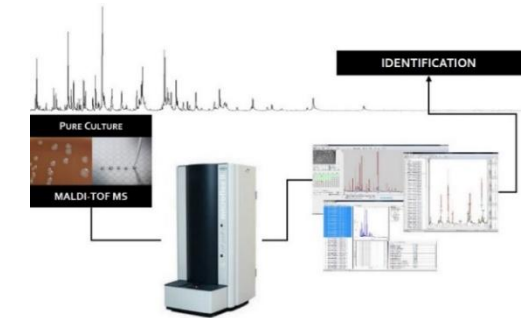
India ink staining



Ag Crypto+++



Culture on SDA-C



Maldi-Tof MS

Review ■

PCR

- Manual diagnostics
- Automatic system: FilmArray®, BioFire, BioMérieux
- Typing

11-12-25



Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM



Christina C Chang, Thomas S Harrison, Tihana A Bicanic, Methee Chayakulkeeree, Tania C Sordell, Adilia Warris, Ferry Hagen, Andriy Spec, Rita Oladade, Nallesh P Govender, Sharon C Chen, Christopher H Modry, Andreas H Groll, Yee-Chun Chen, Michael S Lionakis, Alexandra Alania, Elizabeth Castañeda, Jairo Lizarazo, José E Vidal, Takahiro Takazono, Martin Hoenigl, Jan-Willem Alffenaar, Jean-Pierre Gangneux, Rajeev Saman, Li-Ping Zhu, Alexandro Bonifaz, Joseph N Jarvis, Jeremy N Day, Nikolai Klimko, Jon Salmanton-García, Grégory Jouvion, David B Meyers, David Lawrence, Sebastian Rahn, Felix Bongomin, Brendan J McMullan, Rosanne Sprute, Tinashe K Nyazika, Justin Beardsley, Fabienne Carlesse, Christopher H Heath, Olusola O Ayanlowo, Olga M Mashadi, Flavio Queiroz-Telles Filho, Mina C Hosseini, Atul K Patel, Elvis Terraf, Nina Singh, Oliver A Cornely, David R Boulware, Olivier Lortholary, Peter G Pappas, John R Perfect

Co-influence of cryptococcosis and HIV/AIDS in the DRC

RESEARCH

RESEARCH ARTICLE

HIV EPIDEMIOLOGY

The early spread and epidemic ignition of HIV-1 in human populations

Nuno R. Faria,^{1,2} Andrew Rambaut,^{3,4,5} Marc A. Suchard,^{6,7} Guy Baele,² Trevor Bedford,⁸ Melissa J. Ward,³ Andrew J. Tatem,^{4,9} João D. Sousa,^{2,10} Nimalan Arinaminpathy,¹ Jacques Pépin,¹¹ David Posada,¹² Martine Peeters,¹³ Oliver G. Pybus,^{1*†} Philippe Lemey^{2*†}

Thirty years after the discovery of HIV-1, the early transmission, dissemination, and establishment of the virus in human populations remain unclear. Using statistical approaches applied to HIV-1 sequence data from central Africa, we show that from the 1920s Kinshasa (in what is now the Democratic Republic of Congo) was the focus of early transmission and the source of pre-1960 pandemic viruses elsewhere. Location and dating estimates were validated using the earliest HIV-1 archival sample, also from Kinshasa. The epidemic histories of HIV-1 group M and nonpandemic group O were similar until ~1960, after which group M underwent an epidemiological transition and outpaced regional population growth. Our results reconstruct the early dynamics of HIV-1 and emphasize the role of social changes and transport networks in the establishment of this virus in human populations.

AIDS is one of the most devastating infectious diseases in human history, and its cause, HIV, has been responsible for nearly 75 million infections (1). Shortly after the first reports of AIDS in the United States in

lished in heterosexual populations of central and east Africa (5, 6), suggesting a much older—and, to that point, hidden—history of the pandemic in Africa.

Surveys of African apes identified chimpanzee

50

Notes

Eur. J. Clin. Microbiol.

Clinical Isolates of *Cryptococcus neoformans* from Zaire

D. Swinne^{1*}, J. B. Nkurikiyinfura²,
T. L. Muyembe²

In AIDS patients who are living in or have recently emigrated from Central Africa, the percentage of cases with disseminated cryptococcosis can reach 13% (1), 25% (2) or even more than 35% (3). There are two varieties of *Cryptococcus neoformans* and as both cause cryptococcosis, we found it interesting to determine which variety is responsible for cryptococcosis associated with AIDS.

Cryptococcus neoformans var. *neoformans* is a cosmopolitan variety found in the saprophytic state mainly in bird droppings, especially those from pigeons (4). *Cryptococcus neoformans* var. *gattii* is found only in some well delimited areas (5) and always in the parasitic state. A typical morphological feature of this variety is the presence of elongated cells in addition to the normal round cells (6). *Cryptococcus neoformans* can also be divided into four serotypes: serotypes A and D belong to the variety *neoformans* whereas serotypes B and C belong to the variety *gattii* (7). Since the two varieties have different metabolism a distinction can also be made between the two biovarieties (biovars) according to biochemical criteria.

Making use of these differences, Kwon-Chung (8)

Table 1: Year of isolation and biovariety of 47 clinical isolates from Zaire.

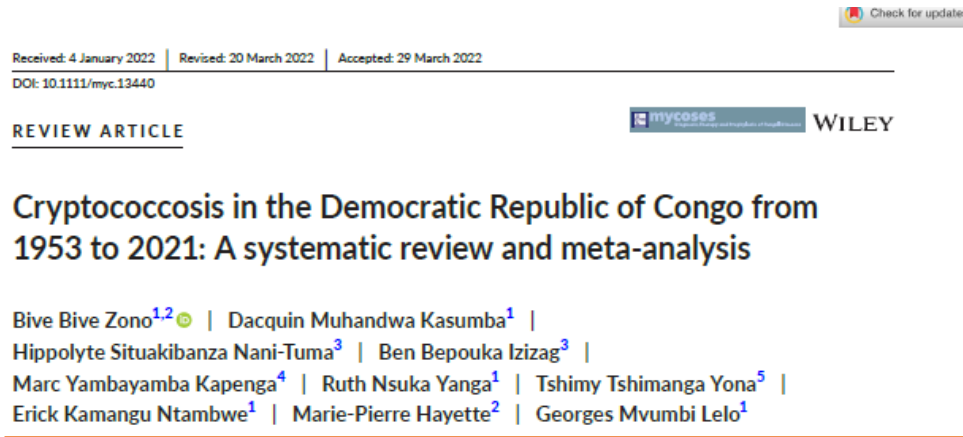
| Year | No. of isolates | Biovar <i>neoformans</i> | Biovar <i>gattii</i> |
|-------------------|-----------------|--------------------------|----------------------|
| 1951 | 1 | 0 | 1 |
| 1953 | 1 | 0 | 1 |
| 1957 | 1 | 0 | 1 |
| 1962 | 1 | 1 | 0 |
| 1966 | 2 | 0 | 2 ^a |
| 1969 | 1 | 0 | 1 |
| 1970 | 2 | 2 | 0 |
| 1977 | 1 | 1 | 0 |
| 1978 | 2 | 2 | 0 |
| 1980 | 1 | 1 | 0 |
| 1981 | 3 | 3 | 0 |
| 1982 | 6 | 6 | 0 |
| 1983 | 12 | 12 | 0 |
| 1984 | 10 | 10 | 0 |
| 1985 ^b | 3 | 3 | 0 |
| Total | 47 | 41 | 6 |

^a One isolate was the type-strain (RV 20186).

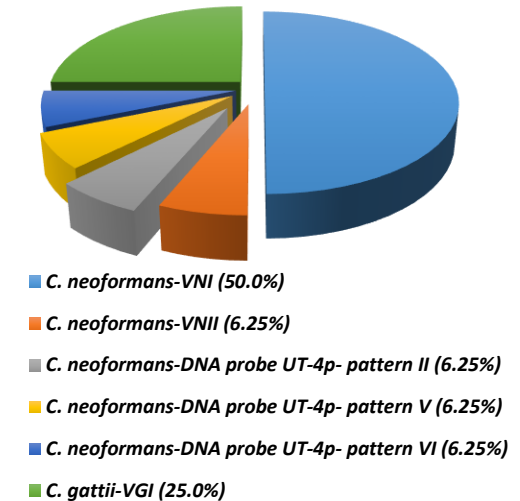
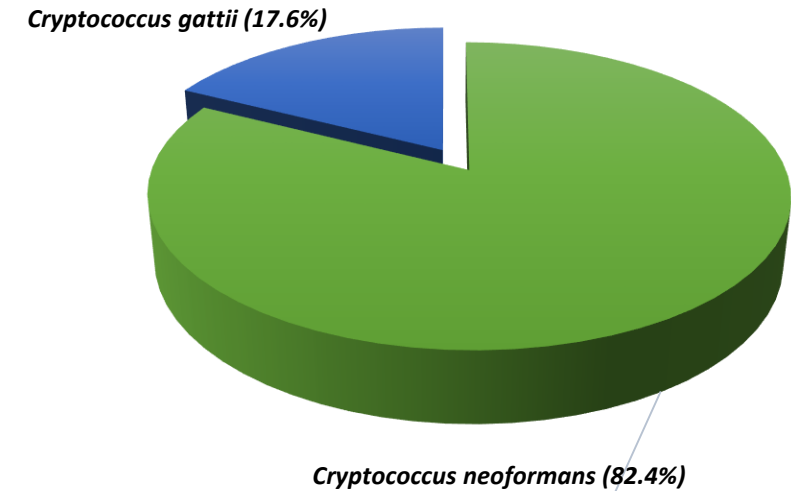
^b Until April 1985.

typical morphology in vivo, i.e. elongated cells present with round cells. All of the 40 isolates collected after 1969 were of the biovar *neoformans*. *Cryptococcus neoformans* biovar *gattii* has thus not been isolated in Zaire during the past 16 years. All African isolates of *Cryptococcus neoformans* var. *gattii* mentioned by Kwon-Chung and Bennett (5) were also recovered before 1970. It therefore seems that *Cryptococcus neoformans* var. *gattii* is disappearing from Central Africa. However, it still exists in North America, Southern Asia, Hawaii, Australia

Retrospective analysis of cryptococcosis in the DRC



- About **1,018** cryptococcosis patients reported in DRC, including **80.8%** with NMC and HIV infected in **97.6%**.
- NMC mean prevalence: **9.63%** (95% CI: 5.99 – 14.07).
- Main treatment: monotherapy with fluconazole.
- **≥ ½ patients (53%)** under treatment died.
- Based on available data, we estimate that **about 9,265** PLHIV suffered from cryptococcosis in 2020, in DRC.
- Among them, about 4,883 would have died in the same year.



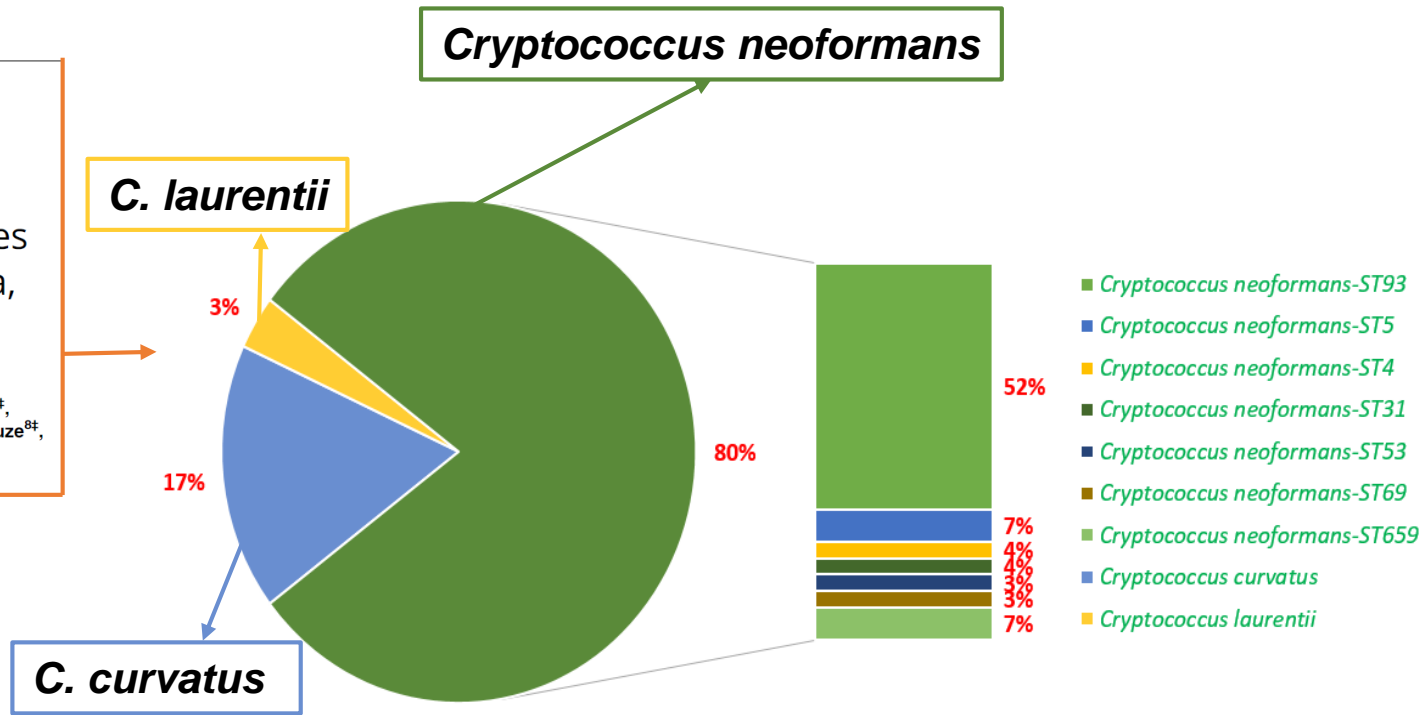
What we currently know about cryptococcosis in DRC? (1)

PLOS ONE

RESEARCH ARTICLE

Clinical epidemiology and high genetic diversity amongst *Cryptococcus* spp. isolates infecting people living with HIV in Kinshasa, Democratic Republic of Congo

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Clinical and biological data

- 66/278 CM among AHD patients (23.7%)
- One AMB resistance: *P. laurentii*.
- Two 5-FU resistance: *P. laurentii* and one *C. neoformans*.
- Four FCZ resistance : two *C. curvatus* and two *C. neoformans*.
- Significative association between poor therapeutic outcome and a non-ST93 sequence type of causative strains.

What we currently know about cryptococcosis in DRC? (2)

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RESEARCH

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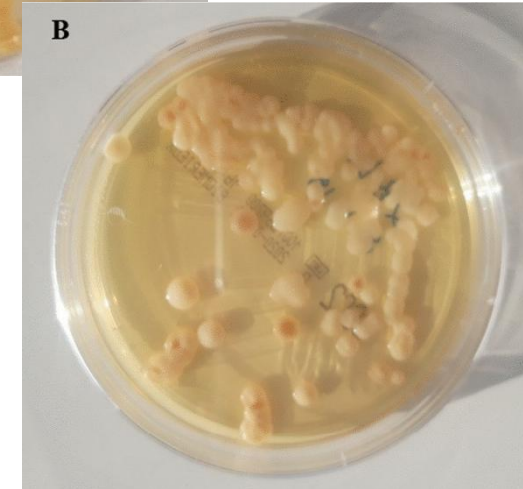
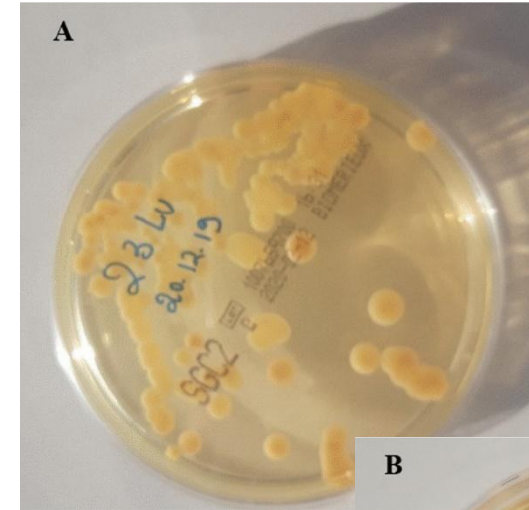


Comparison of clinical and biological characteristics of HIV-infected patients presenting *Cryptococcus neoformans* versus *C. curvatus*/*C. laurentii* meningitis

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- Clinical presentation of *Cn* meningitis was more severe (meningeal signs +++) than that of *Cc/Ci* meningitis.
- Hypoglycorrhachia and low CD4 count were more observed in *Cn* group.
- High antifungals MICs is require for treatment of *Cc/Ci* meningitis versus *Cn*.
- *Cryptococcus* detection by routine analysis was better for *Cn* samples than *Cc/Ci*. Only ITS2 sequencing identified all strains of both groups.
- After treatment with AMB, 5FC, and FLU in both groups, the outcome was similar.

11-12-25



Beige mucoid colonies with reddish hues of *C. curvatus* on SDA-C after 48-h incubation at 30 °C

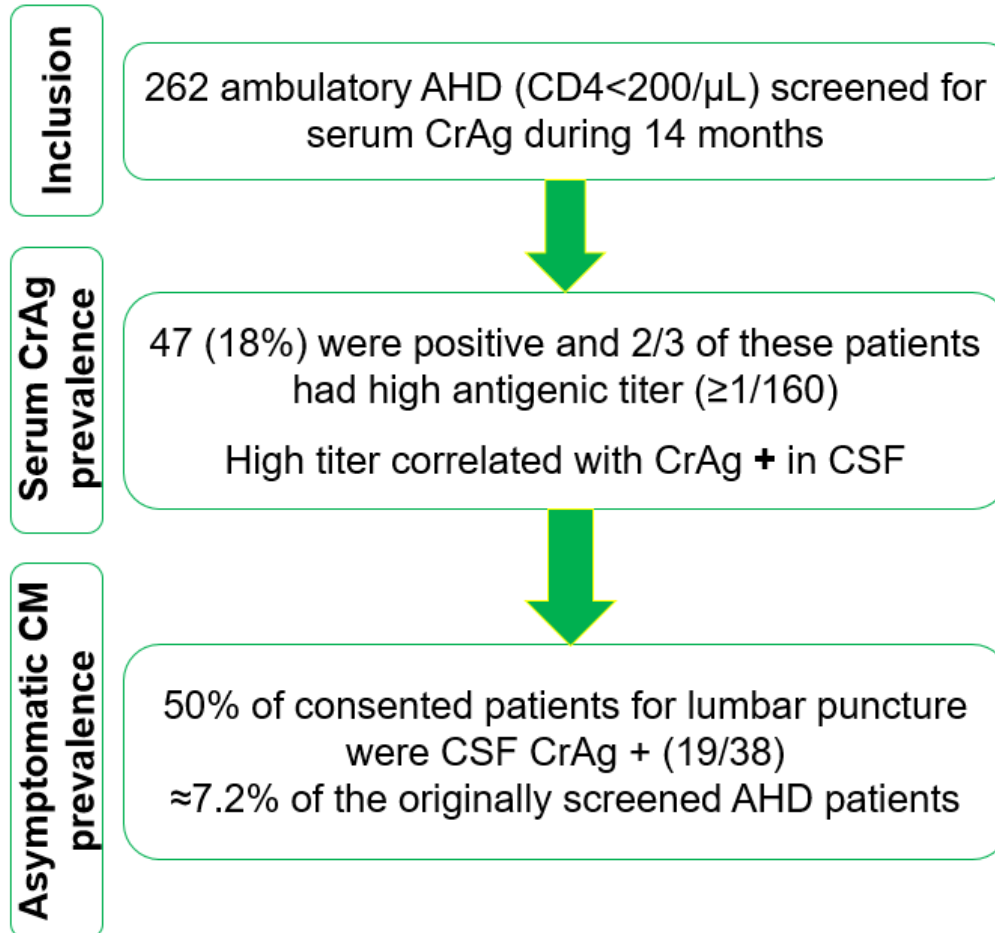
What we currently know about cryptococcosis in DRC? (3)

scientific reports

OPEN **Screening for cryptococcal antigenemia and meningeal cryptococcosis, genetic characterization of *Cryptococcus neoformans* in asymptomatic patients with advanced HIV disease in Kinshasa, Democratic Republic of Congo**

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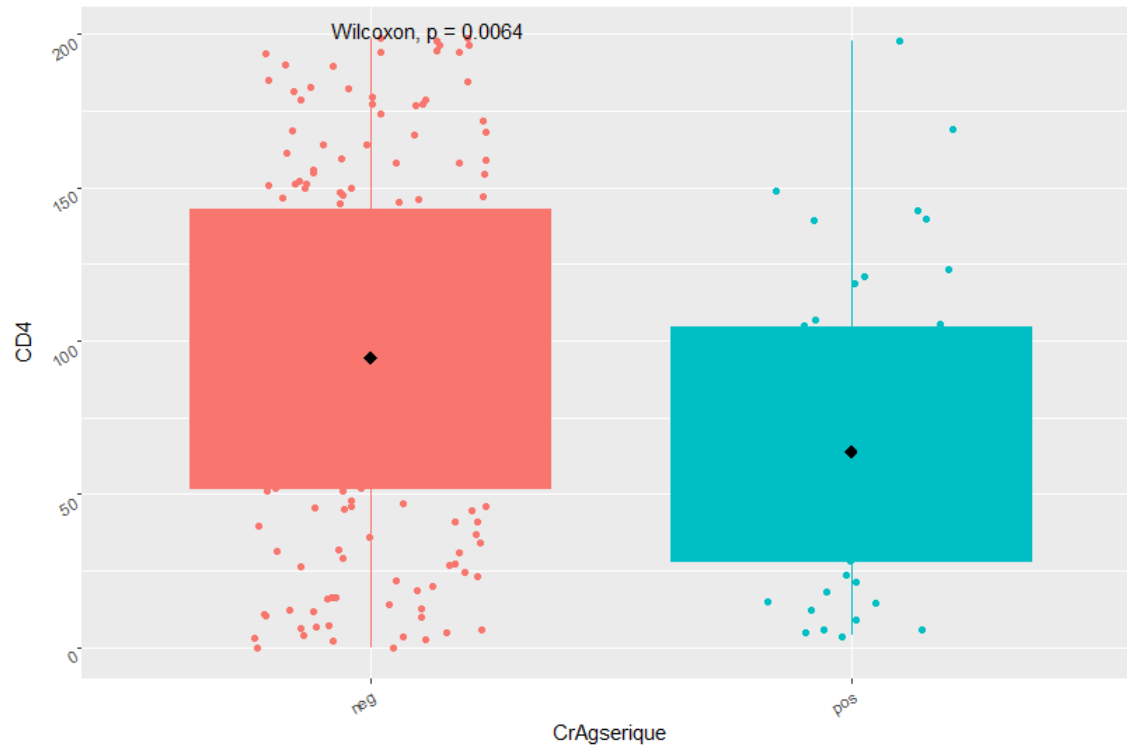
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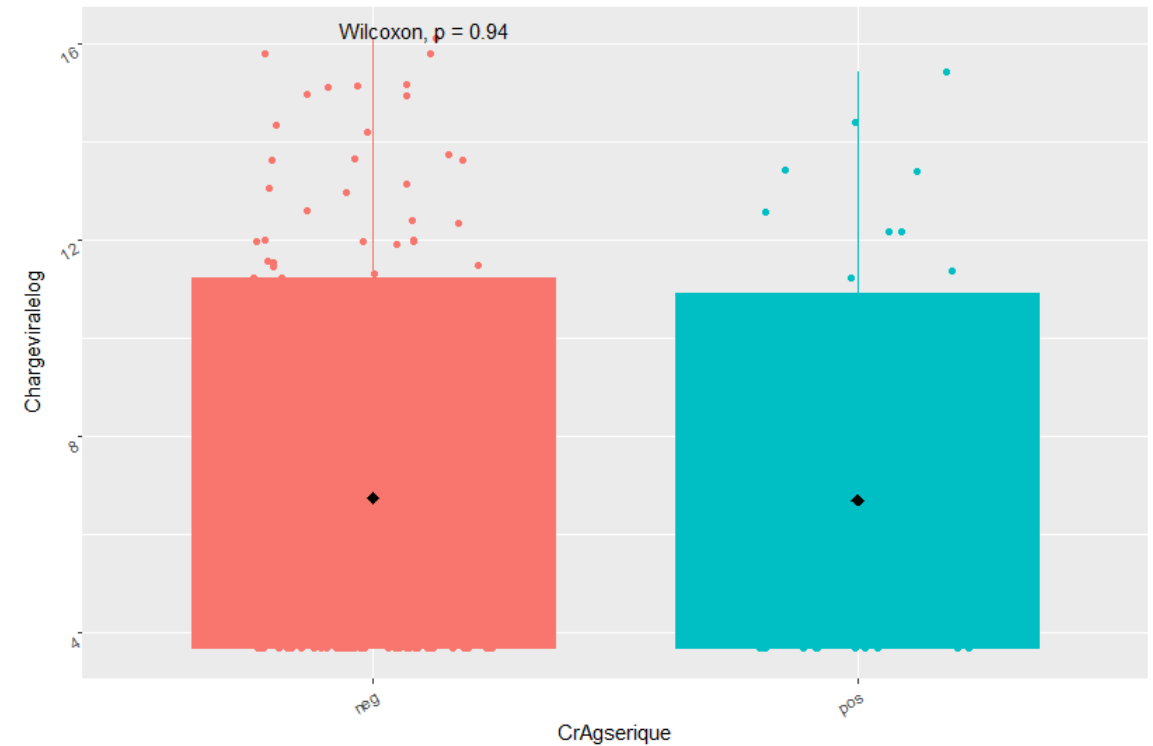
Study flow: inclusion and screening of participants

What we currently know about cryptococcosis in DRC? (4)

CD4 count versus HIV viral load in serum CrAg positive – and in asymptomatic CM patients



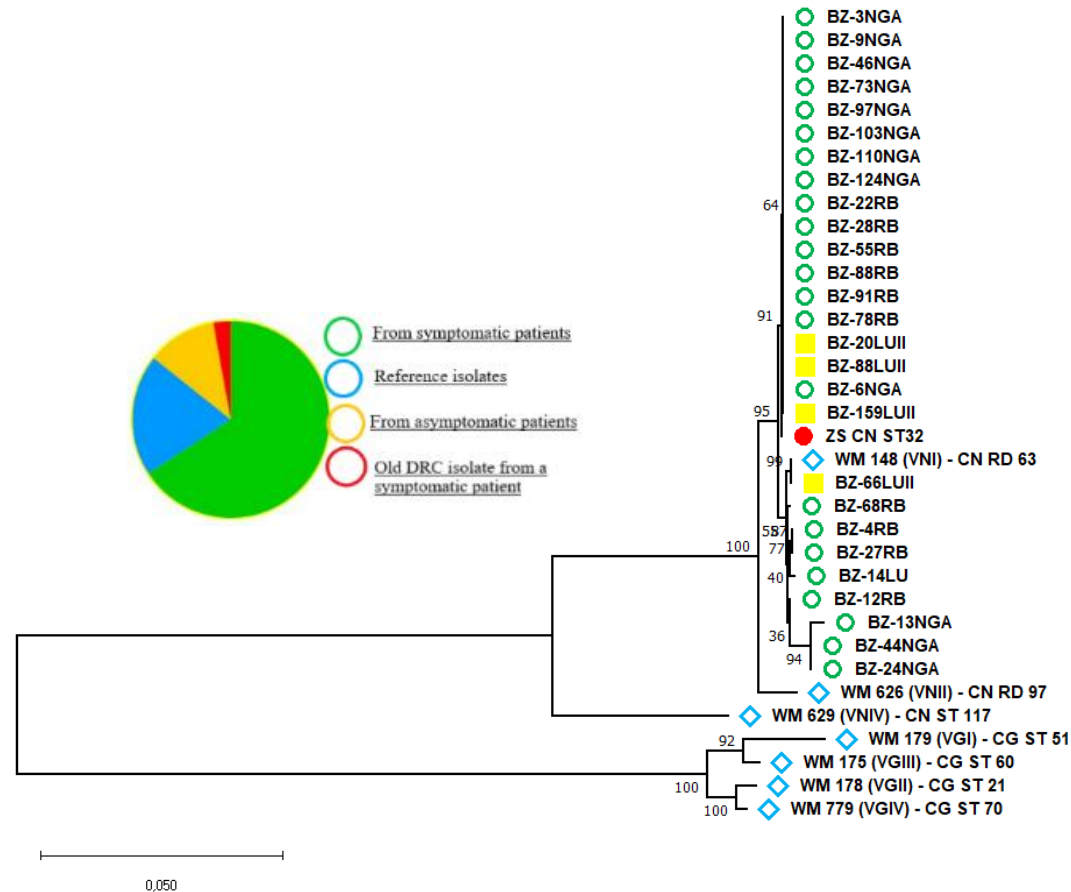
Boxplots of CD4 counts in AHD patients by CrAg serum test (positive ■ versus negative ■)



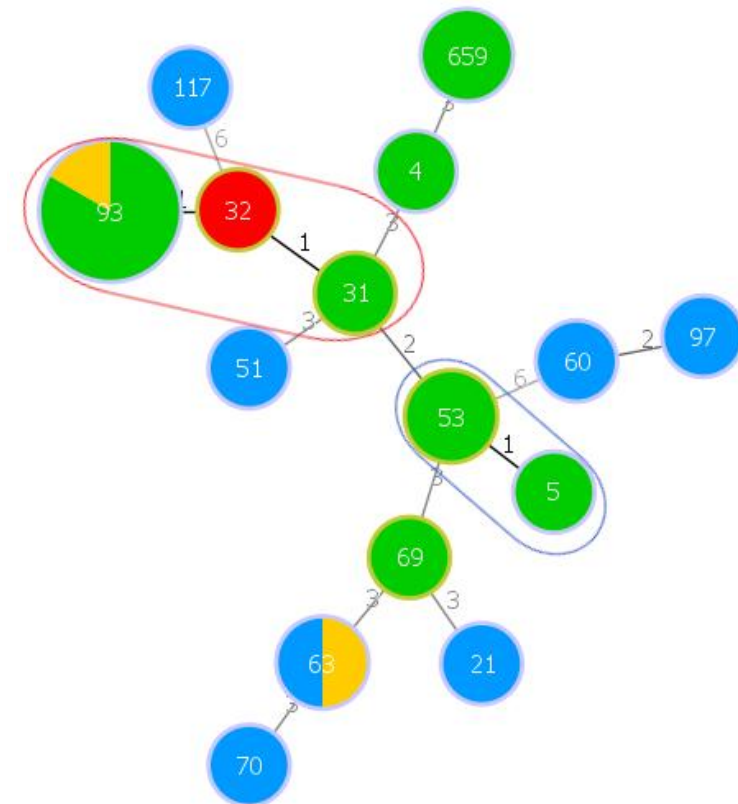
Boxplots of HIV viral load in AHD patients by CrAg serum test (positive ■ versus negative ■)

What we currently know about cryptococcosis in DRC? (5)

Asymptomatic CM is caused by *C. neoformans* isolates similar to those involved in symptomatic patients, unusual ST can also be implicated



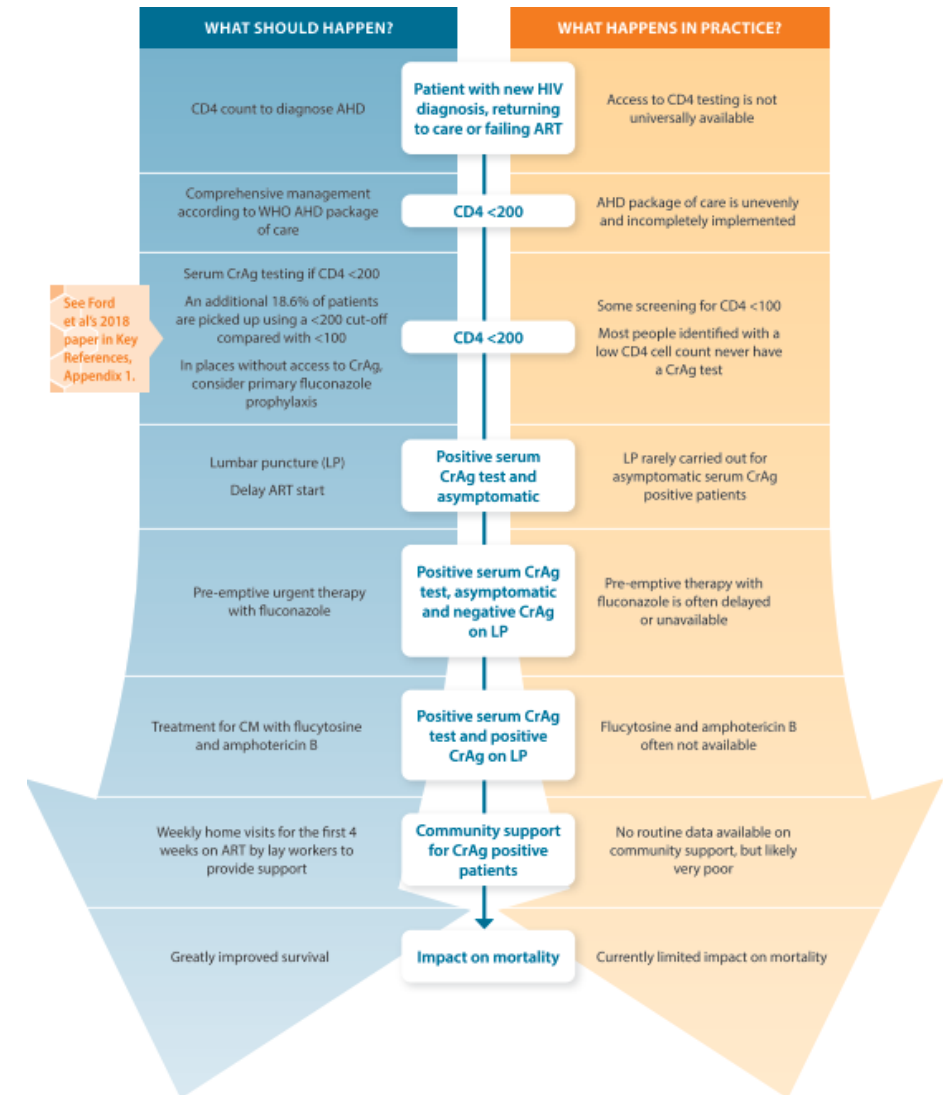
Phylogenetic tree based on the concatenated sequences of the seven MLST loci



Minimum spanning tree based on *Cryptococcus neoformans* ST profile

Perspectives in DRC

- Integrate **active screening of high-risk HIV patients** into the national HIV control program in the DRC
- Conduct further **research into the virulence of *Cryptococcus* strains from the DRC** in order to better plan response measures
- Initiate **research in new antifungal drugs** that are more readily available locally, as current antifungals are already showing resistance
- Also **study other opportunistic fungal infections** that are little known in the DRC with a view to effectively ending HIV-related deaths.



In conclusion ...

- The factors contributing to the **development of fungal infections** are very much present in the DRC, sometimes in **significant proportions**, exposing the country **to a heavy burden**.
- In the **DRC**, the situation regarding cryptococcal meningitis is **worrying** and requires **collective action** [decision-makers – local (government) – global (various donors, etc.) – pharmaceutical industries, etc.] in order to address it.

Thank you for your attention

Congolese Working Group on Mycoses: Activity roadmap



Understanding in order to better fight fungal infections in the Democratic Republic of Congo: a major public health action

