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1 **Estimates of Serious Fungal Infection burden in Côte d'Ivoire and Country Health Profile**

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15 **Key words: fungal disease, Côte d'Ivoire, cryptococcosis, burden disease, histoplasmosis,**
16 **candidiasis, AIDS, TB**

17

18

19 **Abstract**

20 Due to limited access to more powerful diagnostic tools, there are few data on the burden of fungal
21 infections in Côte d'Ivoire, despite a high HIV and TB burden and many cutaneous diseases. Here we
22 estimate the burden of serious fungal infections in this sub-Saharan country with a health profiling
23 description. National demographics were used and PubMed searches to retrieve all published articles
24 on fungal infections in Côte d'Ivoire and other bordering countries in West Africa. When no data
25 existed, risk populations were used to estimate frequencies of fungal infections, using previously
26 described methodology by LIFE (www.LIFE-Worldwide.org).

27 The population of Côte d'Ivoire is around 25 million; 37% are children (≤ 14 years), and 9% are >65
28 years. Tinea capitis in children is common, measured at 13.9% in 2013. Considering the prevalence of
29 HIV infection (2.6% of the population, a total of $\sim 500,000$) and a hospital incidence of 12.7% of
30 cryptococcosis, it is estimated that 4,590 patients per year develop cryptococcosis. For
31 pneumocystosis, it is suggested that 2,640 new cases occur each year with the prevalence of 11% of
32 newly diagnosed HIV adults, and 33% of children with HIV/AIDS. Disseminated histoplasmosis is
33 estimated a 1.4% of advanced HIV disease – 513 cases. An estimated 6,568 news cases of chronic
34 pulmonary aspergillosis (CPA) occur after pulmonary tuberculosis (a 5-year prevalence of 6,568 cases
35 (26/100,000)). Allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal
36 sensitisation (SAFS) were estimated in 104/100,000 and 151/100,000 respectively, in 1,152,178 adult
37 asthmatics. Vulvovaginal candidiasis (VVC) is common and recurrent VVC affects $\sim 6\%$ of women in
38 their fertile years - 421,936 women. An unknown number develop candidaemia and invasive
39 aspergillosis. The annual incidence of fungal keratitis is estimated at 3350. No cases of sporotrichosis,
40 mucormycosis and chromoblastomycosis are described, although some cases of mycetoma and
41 *Conidiobolus* infection have been reported.

42 This study indicates that around to 7.25% (1.8 million) of the population is affected by a serious
43 fungal infection, predominantly tinea capitis in children and rVVC in women. These data should be
44 used to inform epidemiological studies, diagnostic needs and therapeutic strategies in Côte d'Ivoire.

45

46

47 **Introduction**

48 Invasive fungal disease has a high attributable mortality unless diagnosed and treated promptly and
49 appropriately. Nearly 2 million people die from invasive fungal infections each year in the world [1].
50 Over 90% of fungal infection-related deaths are due to species that belong to one of these four
51 genera: *Cryptococcus*, *Candida*, *Aspergillus* or *Pneumocystis*. Epidemiological data for fungal
52 infections are poor because many are misdiagnosed and statistics are extrapolated from few (mostly
53 geographically localized) studies.

54 Côte d'Ivoire (or Ivory Coast) is located in West Africa south of the Sahara between 10 degree North
55 latitude, 4 and 8 degree West longitude. It has an area of 322,462 km² and is bounded to the west by
56 Liberia and Guinea-Conakry, to the north by Mali and Burkina Faso, to the east by Ghana and to the
57 south by the Gulf of Guinea.

58 The population of Côte d'Ivoire is characterized by a growth rate of 2.6% per year and by the high
59 proportion of its youth (41.5%) [2]. The health status of the population is marked by high maternal
60 and infant-juvenile mortality, partly due to inadequate health services. The epidemiological profile is
61 dominated by a high prevalence of HIV among those over 15 years of age as well as a high incidence
62 of malaria among children under 5 and tuberculosis in the population, respectively 2.6% [3], 189.9
63 per 1000 (Annual Report on the Health Situation 2018) and 85 per 100,000 inhabitants (Annual TB
64 notification case 2018) [4]. The national health priorities are these three diseases (HIV, TB and
65 malaria) and recently the novel coronavirus disease 2019 (COVID-19) absorbing all the funds
66 allocated to the health system and hiding the urgency of opportunistic infections such as severe
67 fungal diseases (SFIs).

68 One of the best documented examples of underfunding for fungal diseases is cryptococcosis. This
69 disease is currently responsible for 15%-20% of deaths in individuals with AIDS, and yet in 2015 it
70 received 1% of the funding allocated to tuberculosis [5]. Remedying this situation requires more
71 advocacy by the infectious disease community as well as more studies documenting the local,
72 national and global burden of fungal diseases and their impact on human health.

73 Several studies documenting fungal disease in Côte d'Ivoire are published. Oral *Candida* infections
74 were reported in paediatrics and adult patients [6]. Reports on *Aspergillus* [7, 8] and *Pneumocystis*
75 pneumonia (PCP) infections are limited to few cases [9, 10]. Asthma is the most common chronic
76 respiratory disease with hospitalisation rate of 5% [11] and allergic rhinitis (which may be partly
77 fungal in aetiology) was the most common allergic disease [12].

78 Estimates of the impact of diseases on public health, generally referred to as burden of disease, are
79 valuable inputs for public health authorities, developing appropriate surveillance of fungal diseases
80 and setting policy priorities. Many estimates of the burden of serious fungal diseases are now

81 published for over 60 countries with populations >1 million [13]. Disease burden should be
82 considered as the underlying basis for health care prioritisation in Côte d'Ivoire.

83 Here we report on the burden of fungal disease in Côte d'Ivoire focusing in particular on prevalence data and
84 the reliability of current estimates. These data will contribute to the global SFIs estimation project
85 and awareness campaign, help reframe health policy by bringing a numerical estimate for expanded
86 advocacy, increased research, and improved laboratory diagnostic capacity for the fighting of fungal
87 infection.

88

89 **Methods**

90 The methodology adopted is that previously described [14-16]. Initially, we performed a PubMed
91 search using the Medical Subject Headings terms. Keywords were combined using the Boolean operator
92 AND and OR. Search details are : ("mycoses"[MeSH Terms] OR "mycoses"[All Fields] OR ("fungal"[All Fields] AND
93 "infection"[All Fields]) OR "fungal infection"[All Fields]) AND ("Côte d'Ivoire"[MeSH Terms] OR ("cote"[All Fields] AND
94 "d'ivoire"[All Fields]) OR "Côte d'Ivoire"[All Fields] OR ("ivory"[All Fields] AND "coast"[All Fields]) OR "ivory coast"[All
95 Fields]).

96 Demographic data were obtained from the " Institut National de la Statistique-Côte d'Ivoire" based
97 on the 2014 Housing and Population Census [2]. For many estimations, we used specific populations
98 at risk (HIV/AIDS patients [3], patients with pulmonary TB (PTB) [4], asthma [17], cancer [18], burn
99 patients [4], and patients receiving critical care) to derive national incidence or prevalence estimates
100 of SFIs, using validated data from the country or others nearby, if available. The incidence of chronic
101 superficial mycoses as obtained from those reported in the PubMed-retrieved papers. Cryptococcal
102 meningitis (CM) was estimated in adults only (it rarely occurs in children) at a rate of 12.7% among
103 adult HIV/AIDS patients with CD4 less than 200/ μ L [19]. PCP frequency was estimated by assuming
104 11% of newly diagnosed HIV/AIDS adults (risk spread over 2 years) and 33% HIV/AIDS children at risk
105 (25% of those not on antiretroviral therapy) [20, 21]. Disseminated histoplasmosis was estimated
106 from an autopsy study published in 1994 [22], and assumed to relate to all advanced HIV cases in the
107 country (~80,000) over a 2 year risk period.

108 Regarding invasive fungal Infections associated with hospital care (notably candidiasis and
109 aspergillosis), we considered hematology malignancies [23], lung cancer [18], chronic obstructive
110 pulmonary disease (COPD) [24], ICU and assumed peritonitis surgical patients based on neighbouring
111 country data [25]. No transplantation procedures are currently done in Côte d'Ivoire. For chronic
112 infections, mainly chronic pulmonary aspergillosis (CPA), we used the annual incidence of TB to
113 calculate a annual incidence, as described previously [14-16]. This was then used to compute a five-

114 year prevalence assuming a 15% annual mortality or surgical cure rate. We also assumed that 67% of
115 all CPA cases had prior TB as the underlying disease. Invasive aspergillosis (IA), CPA and allergic
116 bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitization (SAFS) were
117 estimated in adults only. Adult asthma data came from To et *al* as part of the World Health Survey on
118 asthma [17]. We assumed that 2.5% of adult asthmatics had ABPA [26] and 30% of the worst 10% of
119 asthmatics had SAFS, supported by a recent review on asthma in Africa [27].
120 Tinea capitis prevalence was estimated based on a local study in school children [28]. Fungal keratitis
121 annual incidence was extrapolated from East Africa [29].

122 **Results and Discussion**

123 ***Population profile***

124 The total population of Côte d'Ivoire was 22,671,331 inhabitants according to the results of the
125 General Population and Housing Census (RGPH) of 2014. In 2018, it is estimated at 25,195,140
126 inhabitants (the basis of our estimates). About 48.4% are females and ~48% of population live below
127 the poverty line. Poverty is unequally distributed among the regions of Côte d'Ivoire. The level of
128 poverty varies from 22.7% in urban areas to 71.7% in rural areas[30]. Moreover, with the scarcity of
129 public resources, investments in basic social services (health, education, infrastructure, etc.) have
130 fallen considerably, leading to a decrease in the supply of these services. In terms of health
131 resources, Côte d'Ivoire had 2,023 primary health care institutions (PHCI), 82 general hospitals and
132 17 regional hospitals, ie one PHCI for 12,006 inhabitants and one reference hospital for 173,490
133 inhabitants [31].

134 ***Overall disease profile***

135 In 2016, the incidence of endemic diseases (malaria, acute respiratory diseases, HIV/AIDS,
136 tuberculosis) has declined, with the exception of diarrhea and sexually transmitted infections, which
137 are on the rise. The WHO estimated the number of malaria cases at 7,890,000 (5,720,000–
138 10,740,000) in 2016. Since 1995, a National Tuberculosis Program has been established to organize
139 the fight against TB on a national scale. The tuberculosis notification rate in 2016 was 89 notifications
140 per 100,000 inhabitants, compared to 98 per 100,000 inhabitants in 2015. Of 21,299 tuberculosis
141 cases, 4 608 (21.6%) were found to be HIV-positive [31].

142 The total prevalence of HIV infection in 2018 was 2.6% [3]. At the level of care for HIV patients, 44%
143 (1013 sites) of health facilities offered antiretroviral (ARV) care and treatment services. There were
144 252,125 patients on ARVs including 12,347 children (4.9%) and 239,778 adults.

145 With regard to cancer in Côte d'Ivoire, 15,000 new cases are expected each year. Among these
146 cancers It is estimated that 271 cases of lung cancer (5-year prevalence) are diagnosed each year, or
147 1.09 % of all cancers [18, 32].

148 ***Healthcare facility profile and human resources***

149 Côte d'Ivoire registered 6,732 functioning hospital beds in 2018. The estimated number of critical
150 care beds in 2018 was 673 (assuming 10% of hospital beds are occupied by critically ill patients).
151 Transplants programs (solid organ and hematopoietic stem cell) do not exist in Côte d'Ivoire and
152 there is no nationwide registry of surgeries undertaken.

153 In terms of the technical platform and existing health equipment (shown in table 1), there were a
154 total number of 99 operating theaters, 253 public medical biology laboratories, 85 radiology units,
155 629 ambulances and 162 blood transfusion centers in public health establishments in 2018 compared
156 to 2017. However, it should be noted that at the level of health districts: 8.1% register at least one
157 non-functional medical device in their public biology laboratory, 18.6% do not have an operating
158 theater, 26.7% do not have any radiology service and 2.3% do not have a blood transfusion center
159 [4]. Only few (9) centres undertake bronchoscopy with 40% belong to the private sectors and almost
160 all are based in Abidjan.

161 Also in 2018, the Ministry of Health and Hygiene recorded a ratio of physicians providing healthcare
162 in the public sector of 1.4 physicians per 10,000 inhabitants. The ratio of nurses to health care
163 providers in the public sector is 2.3 nurses per 5,000 inhabitants and the ratio of midwives to health
164 care providers in the public sector is 2.7 midwives per 3,000 women of reproductive age (WRA). The
165 WHO minimum standards for human resources in health (1 doctor per 10,000 inhabitants, 1 nurse
166 per 5,000 inhabitants and 1 midwife for 3,000 WRA) were reached in 2018 [31] .

167 Otherwise, the budget granted by the State of Côte d'Ivoire to the Ministry of Health and Public
168 Hygiene fell from USD \$665,138,840 in 2017 to \$650,292,813 in 2018, a decrease of \$14.8 million (-
169 2.22%). This budget represents 5.3% of the general State budget in 2018. This is lower than the
170 commitments made by the State of Côte d'Ivoire at the Abuja (Nigeria) summit in 2001 which is to
171 devote 15% of the general state health budget [31].

172

173 ***Mycology diagnostics***

174 Only few laboratories (5) are capable of doing diagnostic tests for fungal infection with conventional
175 methods (culture, direct examination), antifungal susceptibility testing and/or innovative technical
176 detection or for identification (PCR, MALDI-TOF). India ink microscopy in cerebrospinal fluid is the
177 principal means of making the diagnosis of cryptococcal meningitis. Recent years have seen the

178 introduction of cryptococcal, *Histoplasma* and *Aspergillus* antigen lateral flow assays, as well as ELISA
179 based assays. Only the first is available in Côte d'Ivoire and is not extensively used. An *Aspergillus*
180 antibody point of care assay with excellent sensitivity and specificity [33] has also been launched in
181 the last 2 years and is not yet available. All of these tests are WHO Essential Diagnostics.

182 A solution of choice for the early diagnosis of PCP in health facilities without fiberoptic bronchoscopy
183 is the examination of expectorated sputum or induced by inhalation of a hypertonic solute [34].
184 Detection of *Pneumocystis jirovecii* in sputum or bronchoalveolar lavage fluid can be by direct
185 microscopy using Gomori Methenamine Silver (GMS) or calcofluor white stain, immunofluorescence or
186 PCR. *Pneumocystis* PCR is the most sensitive technique, is now a WHO Essential Diagnostic and is the
187 only means of diagnosing pneumocystosis in children [35]. None these techniques are currently used
188 in Côte d'Ivoire.

189 ***Incidence and prevalence of serious fungal infections***

190 About 7.25% (1,827,204) Ivorians were estimated to be affected by SFIs. Table 2 shows the estimated
191 total burden of fungal infections, the number of infections classified according to the main risk
192 factors as well as the rate for 100 000 inhabitants.

193 ***Candida infections***

194 There are no studies published on candidaemia or invasive candidiasis in Côte d'Ivoire, so we have
195 estimated a general rate of 5/100,000 or 1260 cases of candidaemia annually [36]. Burned patients
196 are more likely to develop candidemia and other fungal systemic lesions, as are HIV positive
197 patients [37]. Candidemia occurs in 2.5 to 7% of patients in intensive care units for burns [38]. In Côte
198 d'Ivoire, the Abidjan center for burn victims receives about 500 burn patients a year. So nearly 25 will
199 develop candidemia [39]. We have assumed that 30% of candidaemia cases occur in intensive care.

200 For surgical ICU patients *Candida* peritonitis may develop in association with recurrent
201 gastrointestinal perforations or anastomotic leakage after surgical intervention. *Candida* species are
202 isolated between 70-90% of all patients with peritonitis [40]. Acute peritonitis is a very common
203 pathology. It occupies third place in acute surgical abdomens after appendicitis and intestinal
204 occlusions. Its frequency is estimated, compared to all acute surgical abdomens, to be 3% in France
205 [41] and 20% in Mali [25]. If as in France we assume that the number of patients with intra-
206 abdominal candidiasis is 50% of those with candidaemia [42], we estimate 189 such cases, but this
207 may be a substantial underestimate.

208 Esophageal candidiasis occur frequently in HIV-infected patients. We estimate 4,665 cases based on
209 20% of new HIV infected patients and 0.5% of those on ARVs [43]. HIV/AIDS adds nearly 2 million
210 cases of oral thrush and >500,000 cases of oesophageal fungal infections annually in the world [44].
211 Oral fungal infections are also common in babies, denture wearers, individuals using inhaled steroids

212 for asthma, leukemia and transplant patients and people receiving radiotherapy for head and neck
213 cancers, but we have been unable to estimate incidence of these cases.

214 rVVC is defined as four or more episodes of vulvovaginal candidiasis per year. This is a surprisingly
215 common health problem in sexually active women. rVVC is relatively common in Côte d'Ivoire with *C.*
216 *albicans* as the main causative agent. In Côte d'Ivoire a cross-sectional study of 400 women attending
217 an STD clinic found – 40% had evidence of VVC [45]. This same cohort was later re-analysed for rVVC
218 and 23.5% of adult women were apparently affected by rVVC [46]. This is however a select
219 population and so the denominator will be larger than 400, but it is not clear how large. Considering the
220 actual adult female population size, our estimate of rVVC prevalence is 421,936 cases of rVVC at a
221 rate of 1,675 females per 100,000 person-years, but the real figure may be higher than this (and we
222 have used 6% in our estimate (Table 2)). About one in four women with VVC developed rVVC, a
223 significantly higher proportion than that reported in the literature, which ranges from 6 to 9% in
224 European and North American women [47, 48]. This relatively high rate seems to corroborate
225 previous studies suggesting an association of rVVCs with the black people [49],[47, 50], suggesting
226 that genetic factors related to being black are responsible for the high susceptibility of women of this
227 racial group to rVVC [50, 51]. However, these putative genetic factors may not explain alone this
228 relatively high rate of rVVC. Host-related and behavioural factors could also be associated with the
229 occurrence of these recurrences.

230 **Fungal related respiratory diseases**

231 Respiratory diseases including TB and asthma are major causes of morbidity and hospital admissions
232 in Côte d'Ivoire. Exacerbations of asthma are common and may be driven by fungi, especially
233 *Aspergillus* spp, which is common in the environment and colonise the airways. ABPA, CPA and SAFS
234 frequencies are thus anticipated to be high. We calculated that SAFS affects 38,022 Ivorian adults
235 annually. ABPA and SAFS are collectively known as “fungal asthma” which is responsive to antifungal
236 therapy, and over 40,000 adults probably suffer from this, as there is probably some duplication
237 between ABPA and SAFS prevalence. The long-term natural history of fungal allergy is not well
238 documented. Some people have allergic fungal infection that comes and goes in severity, usually for
239 unclear reasons. Mucus production and mucosal swelling in the airways, nose and sinuses is the
240 hallmark of fungal allergy.

241 CPA is particularly common after pulmonary TB, and we estimate an annual incidence of 1567
242 cases. However as this is a chronic condition, the overall prevalence will be higher, an estimated
243 6,568, of which 75% of cases are TB related and the remainder to other pulmonary conditions such
244 as sarcoidosis and previous pneumothorax. Some patients have no underlying condition at all, are

245 are usually mis-diagnosed and TB. The key test *Aspergillus* IgG antibody (or precipitins) is not
246 available in Côte d'Ivoire.

247 PCP exists in Côte d'Ivoire as evidenced by the autopsy study of Coulibaly et al. who found in post-
248 mortem a prevalence of 8.6% in 70 HIV-infected patients [22]. This disease is caused by the
249 opportunistic fungus *P. jirovecii*, which is a life-threatening infection in HIV/AIDS patients. Compared
250 with adults, HIV positive children had a high prevalence of *P. jirovecii* pneumonia and a low
251 prevalence of tuberculosis. Almost a third of HIV positive children had PCP, according to Lucas et al.
252 [10], a rate similar to that found in affected children in industrialized countries but much higher than
253 the incidence in adults in Abidjan. We can estimate 2,640 cases of PCP, 990 in adults and 1,650 in
254 children. Several studies from different African countries found the incidence of PCP in HIV-positive
255 patients to vary from 1.25–49% [52].

256 The relative infrequency of pneumocystosis is due to the low prevalence of *Pneumocystis jirovecii* in
257 the African environment and lack of appropriate diagnostic means, such as bronchoalveolar lavage
258 and trans-bronchial biopsy [53]. PCP may occur in other immunosuppression contexts, including solid
259 organ transplant patients (kidney in particular), lymphoma or in patients receiving long-term
260 corticosteroids. In these cases the clinical picture is often more brutal and the symptoms more
261 frequently require admission to intensive care unit. We were unable to assess the incidence of these
262 cases in the absence of any data.

263 Invasive aspergillosis (IA) was estimated in leukaemia, lung malignancies, COPD and HIV/AIDS. It was
264 assumed that 10% of acute myeloid leukaemia (and an equal number of other leukaemia and
265 lymphoma patients), 2.6% of lung cancer patients [54] 1.3% of COPD hospital admissions (65,500)
266 and 4% of HIV/AIDS deaths (16,000) [55] develop IA. We estimate an annual incidence of 1550 cases.
267 Very few of these diagnoses are currently established in Côte d'Ivoire and the optimal therapy of
268 voriconazole is unavailable. Globally over 300,000 individuals develop IA annually with mortality
269 rates ranging between 30% and 95% despite recent advanced HIV disease is a significant risk factor
270 for the development of IA [56, 57]. We know that the diagnosis of IA can be challenging: host risk
271 factors, clinical symptoms and radiological findings must be put into context. Demonstration of
272 morphological features consistent with *Aspergillus* species or recovery of *Aspergillus* from a tissue
273 sample is required to define a positive (definitive) case. Obtaining tissue samples is often problematic
274 in these multi-morbid patients and the yield of fungi in culture is low, difficult to interpret and prior
275 antifungal prophylaxis further reduces its sensitivity [58, 59]. Detection of *Aspergillus* antigen
276 (galactomannan) by ELISA or more recently immune-chromatographic technology (lateral flow
277 devices) have been shown to be much more sensitive than culture [60] but which unfortunately are
278 not yet available in the country. Just as IA cases are challenging to diagnose, so is mucormycosis and
279 we have not estimated this life-threatening infection.

280 **Superficial fungal infections:**

281 Approximately 25% of the general population have superficial fungal infections of skin and nails,
282 that are caused by dermatophytes [61]. Children constitute the most affected population, especially
283 in playgrounds, and thus are more likely to be in closer contact with sources of fungal pathogens.
284 Tinea capitis is very common in children of sub-Saharan countries particularly in Côte d'Ivoire. In a
285 large epidemiology study conducted in 2013, 13.9% of 17,745 children were found to be positive,
286 mainly with anthropophilic dermatophytes, such as *Trichophyton soudanense* and *Microsporum*
287 *langeroni* [28]. We thus estimated that 1,295,786 school children suffer from tinea capitis according
288 to this epidemiological study. A similar pattern and frequency is seen in other West Africa countries
289 including Nigeria [62], Guinea [63] and Senegal [64].

290 Superficial fungal infections are more rarely caused by non-dermatophyte moulds (NDM) attacking
291 the skin or nails. A longitudinal analysis of clinical data in the last 10 years shown the increased
292 prevalence of filamentous fungi involved in superficial mycosis in Côte d'Ivoire. We have recently
293 found *Aspergillus flavus* (24.3%) *Penicillium sp* (22.9%), *Fusarium sp* (17.2%), and *Aspergillus niger*
294 (15.7%) from clinical samples primarily of nails but also intertrigo and mucosal infections (data
295 unpublished). This data was confirmed by a recent review of 42 epidemiological studies from
296 Bongomin et al [65], showed that onychomycosis due to *Aspergillus spp.* varies between <1 and 35%
297 of all cases of onychomycosis in the general population and higher among diabetic populations
298 (accounting for up to 71%) and older people.

299 A single case of *Conidiobolus* infection of the face is described [66]. A small number of mycetoma
300 cases are described [67]. No cases of sporotrichosis or chromoblastomycosis are described. Fungal
301 keratitis is seen clinically but rarely confirmed. Based on a global analysis and using data from East
302 Africa, we estimate 3,351 cases annually. Clearly this needs confirmation and it is likely that all these
303 eyes go blind, or have to be removed.

304 **Cryptococcosis :**

305 The emergence of *Cryptococcus* infections has dramatically changed the epidemiology of cerebro-
306 meningeal disease in sub-Saharan Africa, where 70% of HIV / AIDS infections are concentrated.
307 Neuromeningeal cryptococcosis (NMC) is the most serious form of this infection. Death is inevitable
308 in the absence of antifungal treatment and mortality remains high despite it. The incidence of this
309 pathology varies from 2 to 30% in HIV positive patients. However, epidemiological data of this
310 pathology for Africa are limited. We estimated 4,590 cases of NMC among adult HIV/AIDS patients,
311 using a 12.7% rate from a study Osazuwa et al. [19] However, two hospital-based studies in Côte
312 d'Ivoire [68, 69] reported a surprisingly low prevalence of rate of 0.6 and 3.6 and they cannot be
313 generalized to the population because of selection bias such that many patients with cryptococcal

314 infection probably died before either being tested for HIV or attending the clinic and by the lack of
315 use of cryptococcal antigenemia (CRAg) test which is not yet routinely available in hospitals.
316 Cryptococcal antigenemia (CRAg) is detectable a median of 22 days before the onset of symptoms
317 [70] and was shown to be 100% sensitive for predicting the development of NMC in the first year of
318 ART [71], and is also associated with both NMC and mortality [72]. In view of these observations,
319 screening for subclinical or asymptomatic infection by a serum CRAg assay in patients with advanced
320 HIV infection, and giving antifungal therapy to those testing positive, may prevent the development
321 of NMC.

322 ***Histoplasmosis :***

323 Histoplasmosis is one of the opportunistic infections associated with AIDS. Most diagnoses of
324 histoplasmosis are made post-mortem, as pre-mortem confirmatory tests are unavailable. The
325 autopsy study carried out in Côte d'Ivoire on 70 HIV positive patients who died revealed only 1.42%
326 histoplasmosis [73]. Otherwise histoplasmosis in children or the immunocompetent subject are very
327 rarely described and the clinical presentation is often misleading. But in Côte d'Ivoire two cases of
328 histoplasmosis in immunocompetent patients are recorded : *Histoplasma capsulatum var.*
329 *capsulatum* in a patient 36 years and without blemish [74] and *Histoplasma capsulatum var.duboisii*
330 in a child [75]. We estimate 513 acute disseminated cases based on 1.42% of HIV-infected patients.
331 Our estimate could be an underestimate with a 13% rate of histoplasmosis among HIV-positive
332 patients with persistent fever and coughing associated with cutaneous lesions reported by
333 Mandengue et al. in Cameroon [76] and also the fact that we have a few skilled personnel and
334 facilities to make the diagnosis. In AIDS, 10–40% of patients present with skin lesions, which could
335 facilitate rapid diagnosis if biopsied and examined histopathologically.

336 ***Antifungal therapy***

337 Despite an increase in antifungal treatments over the past two decades, treatment outcomes are still
338 disappointing. Delays in diagnosis and fungal identification greatly limit the efficacy of therapy.
339 Restrictions in route of administration, spectrum of activity, and bioavailability of some antifungal,
340 especially in HIV/AIDS and drug interactions hampers treatment success.

341 There are some antifungal agents available in Côte d'Ivoire that are included in the country's
342 Essential Medicines List (Table 3), including fluconazole, itraconazole, amphotericin B [77]. Many are
343 off patent with numerous generic formulations. Very large numbers of topical azoles are available
344 clinically for thrush and superficial infections; but these are not covered in this report. Conventional
345 amphotericin B treatment is largely used in the hospitalized patient for systemic infection. In
346 Cameroon and Zimbabwe, about 100,000 days of amphotericin B therapy are estimated annually. But
347 in Mozambique and DRC, an estimated 200,000 days of amphotericin B therapy are needed.

348 Flucytosine is not available in Côte d'Ivoire although it has been on the WHO EML since 2013.
349 Itraconazole is not available in Senegal, Gambia, Burundi and Eritrea, and probably some other
350 countries. The total estimated market for itraconazole capsules in Cote d'Ivoire and other antifungals
351 has not been estimated. Natamycin eyedrops is also not available but critically important for fungal
352 keratitis.

353 Because of the increasing of antifungal drug resistance, evidence emphasis on diagnostic testing has
354 several merits. First, it can establish the correct diagnosis, with both immediate and longer term
355 implications for therapy – cryptococcal meningitis being an excellent example. Second, exclusion of a
356 fungal diagnosis can allow stopping of therapy – a good example is discontinuing high dose (and
357 often toxic) cotrimoxazole for PCP [78], as well as corticosteroids. Third, if a fungal diagnosis can be
358 made, instead of a bacterial diagnosis, such as CPA instead of smear negative tuberculosis, then
359 antibacterial therapy can be stopped, contributing to antimicrobial resistance (AMR) control [78].
360 Finally, increasing antifungal resistance, both acquired and intrinsic, allows optimisation of antifungal
361 therapy, instead of blind empiricism before treatment performed.

362

363 **Conclusions:**

364 In conclusion, with almost 1.8 million cases among 25 million people, severe fungal infections affect
365 7.25% of the population of Côte d'Ivoire. This result is comparable to that of Senegal, Ghana and
366 Burkina Faso and other West African countries. Due to the paucity of data, we believe that the true
367 prevalence of fungal infection may still be under-estimated. As in other low and middle income
368 countries, serious fungal infections remain neglected and underestimated in Côte d'Ivoire despite
369 the rising trend globally [79]. Most of these infections are undiagnosed or misdiagnosed leading to
370 no treatment or incorrect treatment. Low indices of suspicion among clinicians and gaps in the
371 availability of diagnostics services and antifungal drugs are the identified causes. Furthermore, the
372 government and public health agencies have paid less attention to fungal infections. Increasing
373 awareness is a significant initial step to change the status quo.

374 There is a need for the national government in Cote d'Ivoire to consider the implications of this
375 increasing disease burden and facilitate better management of health in this neglected and usually
376 vulnerable population. The negative effects of fungal infections on human health are not widely
377 recognized despite the fact that millions of people worldwide will contract life-threatening invasive
378 infections.

379

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594

595 **Table 1 : HealthTechnical platform and equipment available in the country (RASS 2018)**

Technical platform and equipment	2017	2018
Public lab of medical biology	231	253
Operating theater	89	99
ambulance	536	629
Blood transfusion centers	162	162
Radiology department	84	85

596

Table 2: Estimated incidence and prevalence of most serious fungal diseases in Côte d'Ivoire.

infection	Number of infection per underlying disorder per year					Total burden	Rate/100K
	None	HIV/AIDS	Respiratory	Cancer	ICU		
Esophageal candidiasis	-	4,665	-	-	-	4,665	19
Oral candidiasis	-	17,280	-	-	-	17,280	69
Candida peritonitis	-	-	-	-	189	189	0.75
Candidaemia	-	-	-	882	378	1260	5
Recurrent candida vaginitis (4x/year)	421,936	-	-	-	-	421,936	1,675
ABPA	-	-	28,804	-	-	28,804	114
SAFS	-	-	38,022	-	-	38,022	151
CPA	-	-	6,568	-	-	6,568	26
Invasive aspergillosis	-	640	852	58	-	1,550	6.15
Cryptococcal meningitis	-	4,590	-	-	-	4,590	18.22
Pneumocystis pneumonia	-	2,640	-	-	-	2,640	10.48
Histoplasmosis	-	513	-	-	-	513	2.04
Tinea capitis	1, 295,786	-	-	-	-	1, 295,786	5,143
Fungal keratitis	3,350	-	-	-	-	3,350	13.3
Total burden estimated	1, 721,072	30,328	74,246	940	567	1, 827,204	

Allergic bronchopulmonary aspergillosis : ABPA ; Severe asthma with fungal sensitisation : SAFS ; chronic pulmonary aspergillosis : CPA ;

Intensive care Unit : ICU

Table 3 : Antifungal agents available in Côte d'Ivoire and whether included in the Essential Medicines List

Antifungal agent	Available	On EML	Hospital use	Community pharmacy availability
<i>Systemic agents</i>				
Amphotericin B	Yes	Yes	Yes	Yes
Lipid amphotericin B	No	-	-	-
Fluconazole	Yes	Yes	Yes	Yes
Itraconazole	Yes	Yes	No	Yes
Ketoconazole	Yes	Yes	Yes	Yes
Terbinafine	Yes	Yes	Yes	Yes
Griseofulvin	Yes	Yes	Yes	Yes
Flucytosine	No	-	-	-
Voriconazole	No	-	-	-
Caspofungin	No	-	-	-
Micafungin	No	-	-	-
Anidulafungin	No	-	-	-
<i>Topical agents</i>				
Natamycin eye drops	No	-	-	-
Nystatin	Yes	-	Yes	Yes
Miconazole	Yes	Yes	Yes	Yes
Econazole	Yes	No	Yes	Yes
Cyclopiroxolamine	No	-	-	-

EML = WHO Essential Medicine List