Appendix 1

Lima Peru 3-5 September 2019

GLOBAL FUNGAL INFECTION FORUM 4

THE BURDEN OF SERIOUS FUNGAL INFECTIONS IN LATIN AMERICA

95/95 BY 2025

gaffi GLOBAL ACTION FUND FOR FUNGAL INFECTIONS

The burden of serious fungal infections in Latin America

Most life-threatening fungal infections are not diagnosed by conventional culture, microscopy and histopathology. There have a been major developments in rapid and sensitive diagnostics for fungal diseases in the last few years and so it should be possible to diagnose the vast majority of these life-threatening fungal diseases. Without appropriate treatment, death is the usual outcome; or for chronic infections, continued chronic ill health and the risk of death. In most countries, the 'diagnostic gap' is large. Surveillance programs are rare. For these reasons, the incidence and prevalence (combined = burden) of the most serious fungal diseases are poorly documented in most countries for most diseases.

This summary document provides country estimates for the most important serious fungal diseases in Latin America, using consistent baseline data on underlying disorders and methodology, and all accessible local publications. The purpose of this document is to provide a basis for planning for diagnostic tests (and antifungal therapy) implementation, in each country. These estimates are just that, estimates, and as such will not be precise. Changes over time are inevitable, because medical practice influences the frequency of underlying conditions which favour the development of serious fungal diseases, as well as the emergence of antifungal resistance and outbreaks.

95/95 BY 2025

HIV-related fungal infections

Cryptococcal meningitis

Cryptococcal infection is acquired through inhalation and occasional cases of cryptococcal pneumonia or lung nodule are diagnosed. Much more commonly it leads to meningitis, primarily in AIDS, but also in other immunocompromised people and rarely in those without a known immune deficit.

In the table below we have estimated the number of cases of cryptococcal meningitis in each Latin American country. We have assumed the following:

1. Patients not on antiretroviral therapy (ARVs) are at risk with a CD4 count <200/uL, and we have assumed a 7 year decline of CD4 cells to <200/uL for those not on ARVs. We have added an additional 15% to account for those who just started ARVs and defaulters. The % of Venezuelans on ARVs is from 2016.
2. UNAIDS HIV figures for 2017 were used.
3. The proportion of those CrAg positive with CD4 cells <100/uL are taken from Rajasingham (2017), Riera (2018) for Argentina, Borges (2019) for Brazil and unpublished data from Guatemala (Samayoa) which has been applied to central America and Venezuela (but not Mexico).
4. That 76% of cases occur in HIV patients, based on data from Colombia (Noguera, 2019).
5. That the mortality is 40% based on a recent multi-country survey from Argentina, Brazil, Chile, Honduras and Mexico (Crabtree Ramirez, 2017).

Table 1. See page 4

Pneumocystis pneumonia (PCP)

Pneumocystis jirovecii is a human-only pulmonary pathogen transmitted early in life and then repeatedly. Immunity is limited and immunosuppressed patients are susceptible to infection from new genotypes. It is not culturable and so is diagnosed by microscopy or PCR on respiratory specimens, or circulating B-D-1.3 glucan levels. Patients often have distinctive findings on chest CT scan. Prophylaxis with cotrim is effective, but protection is not complete. The survival rate in HIV patients with good treatment is 70-90%, but only 50% in non-HIV patients. Corticosteroid adjunctive therapy reduces mortality in HIV patients but not in HIV negative people.

AIDS-related PCP in adults from Latin American countries has a variable incidence - from 5.9 to 55% (Calderon, 2013). Some studies are done in newly presenting HIV patients, others in those presenting with respiratory symptoms and others are autopsy series. Those reporting rates for all inpatients are most useful for our estimating purpose, namely Villais-Keever (2001) (Mexico - 24.8%), Perez (2005) (Argentina – 9.4%), Neres Norberg (2009) (Brazil – 26.3%), Soares (2008) (Brazil – 22.2%), Diaz (2018) (Brazil – 10.8%). The last study was prospective in already diagnosed HIV patients followed up in SW Goais, Brazil, and therefore the 10.8% incidence represents ARV experienced patients, rather than newly presenting patients.

In the table below are shown the estimated cases of PCP by country in HIV and non-HIV patients. The assumptions are:

1. UNAIDS HIV figures for 2017 were used.
2. Patients not on antiretroviral therapy (ARVs) are at risk with a CD4 count <200/uL, and we have assumed a 7 year decline in CD4 count in those not on ARVs. We have added an additional 15% to account for those who just started ARVs and defaulters.
3. Non-HIV patients with PCP is based on experience that 22% of newly presenting patients with HIV and low CD4 counts develop PCP, based on a rough mean of the above studies.
4. That based on experience from Venezuela of 30 patients diagnosed with PCP at the Instituto Nacional de Higiene Rafael Rangel, 60% of patients had disorders other than HIV (Panizo, 2008).
5. Mortality is 30% in HIV and 50% in non-HIV patients.

Table 2. See page 5

See here for more information about cryptococcal meningitis and PCP:
www.gaffi.org/media/fact-sheets

Table 1. Cryptococcal meningitis cases in Latin America.

Country	Total HIV	% on ARVs	HIV not on ARVs	HIV population at risk 15%*	CrAg % <100 CD4	CM cases HIV	CM total	Deaths (40%)
Argentina	140,000	61	55,000	9,036	8	732	981	392
Bolivia	22,000	44	12,100	1,988	5	97	131	52
Brazil	900,000	66	310,000	50,929	8	4,023	5,391	2,157
Chile	71,000	63	26,000	4,271	5	209	280	112
Colombia	160,000	73	50,000	8,214	7	581	778	311
Costa Rica	15,000	49	7,800	1,281	9	118	158	63
Cuba	31,000	75	9,000	1,479	5	72	97	39
Dominican Republic	70,000	56	31,000	5,093	5	250	334	134
Ecuador	44,000	57	19,000	3,121	5	153	205	82
El Salvador	25,000	47	13,000	2,136	9	196	263	105
Guatemala	47,000	43	27,000	4,436	9	408	547	219
Honduras	23,000	50	11,000	1,807	9	166	223	89
Mexico	230,000	70	70,000	11,500	5	564	755	302
Nicaragua	9,400	53	4,409	724	5	35	48	19
Panama	26,000	54	12,000	1,971	9	181	243	97
Paraguay	21,000	40	12,500	2,054	5	101	135	54
Peru	79,000	73	21,000	3,450	4	124	166	67
Uruguay	14,000	58	5,900	969	5	47	64	25
Venezuela	120,000	61	46,800	7,689	9	707	948	379
Totals	**2,047,400**		**743,509**	**122,148**		**8,766**	**11,747**	**4,699**

* This 15% corresponds to non-compliant patients, those with resistant HIV and patients who have recently initiated ARV therapy.

Table 2. PCP in Latin America.

Country	Total HIV	% on ARVs	HIV not on ARVs	HIV population at risk 15%*	PCP cases in HIV	PCP cases in non-HIV	Total PCP cases	PCP Deaths
Argentina	140,000	61	55,000	9,036	1,988	2,982	4,970	2,087
Bolivia	22,000	44	12,100	1,988	445	668	1,113	468
Brazil	900,000	66	310,000	50,929	11,060	16,590	27,649	11,613
Chile	71,000	63	26,000	4,271	949	1,424	2,374	997
Colombia	160,000	73	50,000	8,214	1,561	2,342	3,903	1,639
Costa Rica	15,000	49	7,800	1,281	276	415	691	290
Cuba	31,000	75	9,000	1,479	280	420	700	294
Dominican Republic	70,000	56	31,000	5,093	1,113	1,670	2,783	1,169
Ecuador	44,000	57	19,000	3,121	684	1,026	1,710	718
El Salvador	25,000	47	13,000	2,136	479	718	1,197	503
Guatemala	47,000	43	27,000	4,436	968	1,452	2,421	1,017
Honduras	23,000	50	11,000	1,807	416	623	1,039	436
Mexico	230,000	70	70,000	11,500	2,494	3,741	6,235	2,619
Nicaragua	9,400	53	4,409	724	160	240	399	168
Panama	26,000	54	12,000	1,971	432	648	1,081	454
Paraguay	21,000	40	12,500	2,054	455	683	1,139	478
Peru	79,000	73	21,000	3,450	771	1,156	1,927	809
Uruguay	14,000	58	5,900	969	213	319	531	223
Venezuela	120,000	61	46,800	7,689	1,691	2,537	4,229	1,776
Totals	**2,047,400**		**731,438**	**120,165**	**26,436**	**39,654**	**66,091**	**27,758**

* This 15% corresponds to non-compliant patients, those with resistant HIV and patients who have recently initiated ARV therapy.

Disseminated histoplasmosis in AIDS

Progressive disseminated histoplasmosis is an increasingly commonly recognized cause of infection in patients with advanced HIV disease from areas endemic for histoplasmosis. The Guiana Shield and Guatemala are hyper-endemic areas (Medina, 2017). Only Chile, Uruguay and Paraguay are low endemicity areas.

Disseminated histoplasmosis often resembles and can be misdiagnosed as tuberculosis in AIDS and is a major cause of death among HIV patients. The presence of skin lesions, which can be biopsied, is helpful if present. Gastrointestinal symptoms are often prominent in disseminated histoplasmosis, unlike in tuberculosis. Pancytopenia is more profound than in other patients with advanced HIV disease. Histoplasma antigen can be detected in the urine of 95-100% and in the serum of 80% of patients with disseminated histoplasmosis (Nacher, 2018) – alternative means of establishing the diagnosis include bone marrow or skin biopsy, blood film (40% sensitivity) and PCR – culture is insensitive and too slow.

The burden and likely mortality of disseminated histoplasmosis in AIDS has recently been assessed for Latin America (Adenis, 2018). We have used these estimates and augmented them with a 3% and 5% risk for Cuba and Dominican Republic below.

The key assumptions made in generating these estimates were directly taken from Adenis et al, (2018):

1. Histoplasma exposure prevalence in the general population was assessed based on existing literature - 24 articles representing 129 histoplasmin skin test studies in the general population of Latin American countries
2. Histoplasma skin test positive prevalence was assumed to be similar in the general population and those with HIV infection.
3. Annual incidence of disseminated histoplasmosis in HIV patients was calculated for each country and adjusted for those with <200/uL CD4 cells.
4. UNAIDS HIV figures for 2012 were used.
5. Adenis et al described a range of incidence from 30-70% and mortality of 20-60%. Here we show the 50% incidence estimate and 60% mortality estimate, assuming that many diagnoses are never made and the mortality is 100% in these patients.

Fig 1. See Page 7

Table 3. See Page 8

See here for more information about disseminated histoplasmosis:
www.gaffi.org/media/fact-sheets

Median prevalence of previous exposure to *Histoplasma capsulatum*

- >40%
- 30-40%
- 20-30%
- <20%

Fig 1

Table 3. Estimates of the number of cases of disseminated histoplasmosis in AIDS by Latin American country in HIV, and deaths compared with tuberculosis.

Country	Total HIV	% on ARVs	HIV not on ARVs	HIV population at risk 15%*	Histoplasmosis cases in HIV	Histoplasmosis deaths in HIV	TB cases in HIV	TB deaths in HIV
Argentina	140,000	61	55,000	9,036	932	559	280	52
Bolivia	22,000	44	12,100	1,988	70	42	420	140
Brazil	900,000	66	310,000	50,929	2,357	1,414	14,000	2,200
Chile	71,000	63	26,000	4,271	1	-	51	8
Colombia	160,000	73	50,000	8,214	782	469	1,400	310
Costa Rica	15,000	49	7,800	1,281	89	53	61	10
Cuba	31,000	75	9,000	1,479	44	27	98	12
Dominican Republic	70,000	56	31,000	5,093	255	153	1,200	250
Ecuador	44,000	57	19,000	3,121	254	153	1,200	390
El Salvador	25,000	47	13,000	2,136	330	198	220	29
Guatemala	47,000	43	27,000	4,436	1,338	803	900	410
Honduras	23,000	50	11,000	1,807	259	155	460	110
Mexico	230,000	70	70,000	11,500	794	477	2,500	430
Nicaragua	9,400	53	4,409	724	89	54	110	17
Panama	26,000	54	12,000	1,971	142	85	280	47
Paraguay	21,000	40	12,500	2,054	45	27	280	57
Peru	79,000	73	21,000	3,450	346	208	2,400	450
Uruguay	14,000	58	5,900	969	24	14	130	20
Venezuela	120,000	61	46,800	7,689	1,622	973	1,200	330
Totals	**2,047,400**		**743,509**	**122,148**	**9,773**	**5,863**	**27,190**	**5,272**

* This 15% corresponds to non-compliant patients, those with resistant HIV and patients who have recently initiated ARV therapy.

Invasive aspergillosis in AIDS

Invasive aspergillosis (IA) in HIV patients is more commonly found in those on corticosteroids or with neutropenia but occurs at any level of CD4 count. It is usually a subacute illness occurring over 3-12 weeks. The diagnosis can be difficult as the radiological and clinical features are similar to other infections. It is often mistaken for tuberculosis, as cavitation is common on chest imaging. *Aspergillus* antigen, possibly *Aspergillus* antibody, and lung biopsy are the usual means of establishing the diagnosis.

Many autopsy series have found about ~4% of deaths are attributable to IA (range 0-12%). In Latin America, the prevalence at autopsy was 2.7% among 74 paediatric autopsies (Drut, 1997), 3.5% in 211 autopsies in Cuba (Arteaga Hernandez, 1998), 12.5% of 16 autopsies in Peru (Eza, 2006) and 0.4% in a 250-autopsy series in Brazil (Soeiro, 2008). Based on these autopsy series from Latin America we have assumed that 4% are affected. Therefore, we have calculated that IA is the primary cause of death in HIV in 1,364 people (Table 5). In countries where the UNAIDS figures are incomplete we assumed that 5% of those not on ARVs die annually (range 3-8%).

Other fungal infections

Oesophageal candidiasis is common in late stage HIV, affecting about 20% of those with a CD4 count <200/uL and about 5% of those on ARVs (Smith, 1990; Buchacz, 2010). Patients present with dysphagia, nausea, vomiting and loss of appetite and chest pain. It has a major impact on patients' nutritional status. It may be recurrent. In Latin America, this translates to ~90,000 cases, 24,500 in those not on ARVs and 65,200 in those receiving ARVs. Fluconazole resistance occurs in 3-7% of *Candida albicans* from HIV patients and becomes increasingly common with recurrent therapy, so ~4,500 patients will likely have fluconazole resistant therapy, requiring itraconazole solution or intravenous therapy.

Coccidioidomycosis

Coccidioidomycosis is an occasional HIV-related infection, but its frequency in Latin America is not clear. Individual cases reports are described. In Mexico, an estimated 8552 cases of coccidioidomycosis occur annually (probably an under-estimate) (Corzo-Leon, 2015), but the proportion in HIV patients is not clear.

Endemic area

Map from: http://life-worldwide.org/fungal-diseases/coccidioidomycosis

Fig 2.

Paracoccidioidomycosis

Paracoccidioidomycosis (PCM) also occurs in some patients with HIV and AIDS. PCM is an endemic airborne fungal infection is limited to central and South America. It is not more frequent in HIV-infected individuals but the clinical course in co-infected patients tends to be more severe. In a 2009 retrospective case control study, the mortality in HIV positive PCM patients was 12.2% (directly attributable to PCM, 24.4% all-cause mortality) compared to 6% in HIV negative PCM patients (Morejon, 2009). PCM has been adopted by the WHO as a Neglected Tropical Disease.

- **Regions of lowest incidence**
- **Regions of moderate incidence**
- **Regions of highest incidence**

See: www.gaffi.org/where/neglected-fungal-diseases and Appendix 2 for more information

Map from: http://life-worldwide.org/fungal-diseases/paracoccidioidomycosis

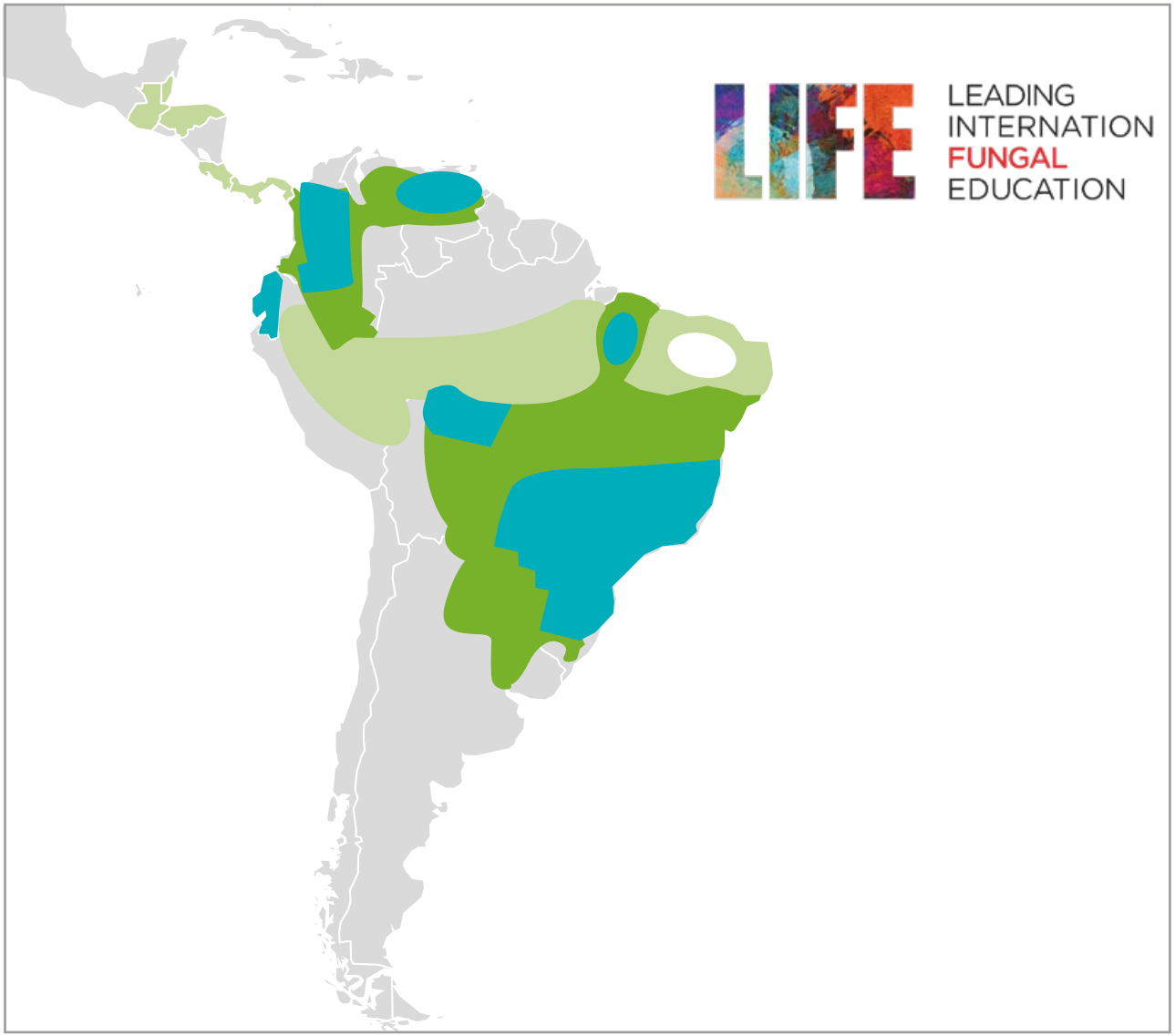


Fig 3.

Life-threatening infections in hospitalised patients and critical care

Candidaemia and invasive candidiasis

Bloodstream infections caused by *Candida* are relatively common and amongst the most lethal of causes of sepsis. Patients at risk include premature neonates, adult and paediatric ICU patients, those with diabetes, renal dysfunction, on total parenteral nutrition, after major surgery or pancreatitis and following multiple classes of antibiotics. Outbreaks are described, including one in Costa Rica caused by *Candida parapsilosis*, with a 50% mortality (Villalobos, 2016). Many different species of *Candida* are implicated, some of which are fluconazole resistant and less commonly echinocandin resistant. The new pathogen *Candida auris* has the propensity for outbreaks (as in Venezuela) (Calvo, 2016) and can be multidrug resistant. The benefits of antifungal therapy was demonstrated in a paediatric multi-country survey in which mortality fell from 72% to 24% with antifungals in neonates (Santolaya, 2014).

A small number of epidemiology studies have defined the annual incidence in some countries and areas. These include Brazil at 14.9/100,000 (Giacomazzi, 2016), Colombia at 12.8/100,000 (Alvarez-Moreno, 2018), Ecuador 0.9/1,000 admissions (Zurita, 2017), Uruguay 0.75–1.64/1000 (Macedo-Viñas, 2018) and Venezuela 16/100,000 (Dolande, 2017). Using these estimates and annual incidence figures of 5/100,000 (low), 10/100,000 (mid) and 15/100,000 (higher), we have estimated cases of candidaemia per year by country (Table 4). The low/mid estimate for Mexico is in accord with a recent epidemiological study from 4 hospitals (Corzo-Leon, 2018).

Blood cultures are about 40% sensitive for detecting invasive candidiasis (Berenguer, 1993; Avni, 2011; Nguyen, 2012). In a large series of surgical intra-abdominal candidiasis *(Candida peritonitis)*, only 6% of cases had a positive blood culture for *Candida* (Vergidis, 2016). Fluconazole therapy reduces the yield from blood cultures (Kami, 2002). So we have assumed that the actual incidence of invasive candidiasis (IC) (including intra-abdominal candidiasis) is 2.5 x that of documented candidaemia (Table 4).

Table 4. See page 13

Table 4. Candidaemia and invasive candidiasis

Country	Population 2017 *	Rates 100,000	Candidaemia cases	Invasive candidiasis cases	Rates 100,000	Candidaemia cases	Invasive candidiasis cases	Rates 100,000	Candidaemia cases	Invasive candidiasis cases
		Low estimate			Mid estimate			Higher estimate		
Argentina	44.27	5	2,214	5,534	10	4,427	10,625	15	6,641	16,601
Bolivia	11.05	5	553	1,381	10	1,105	2,652	15	1,658	4,144
Brazil	209.30	14.9	31,186	77,964	14.9	31,186	74,846	14.9	31,186	77,964
Chile	18.05	5	903	2,256	10	1,805	4,332	15	2,708	6,769
Colombia	49.07	12.8	6,281	15,702	12.8	6,281	15,074	12.8	6,281	15,702
Costa Rica	4.91	5	245	613	10	491	1,177	15	736	1,840
Cuba	11.48	5	574	1,435	10	1,148	2,755	15	1,722	4,305
Dominican Republic	10.77	5	539	1,346	10	1,077	2,585	15	1,616	4,039
Ecuador	16.62	6.2	1,030	2,576	6.2	1,030	2,473	6.2	1,030	2,576
El Salvador	6.38	5	319	797	10	638	1,531	15	957	2,392
Guatemala	16.91	5	846	2,114	10	1,691	4,058	15	2,537	6,341
Honduras	9.27	5	463	1,158	10	927	2,224	15	1,390	3,474
Mexico	129.20	5	6,460	16,150	10	12,920	31,008	15	19,380	48,450
Nicaragua	6.22	5	311	777	10	622	1,492	15	933	2,332
Panama	4.10	5	205	512	10	410	984	15	615	1,537
Paraguay	6.81	5	341	851	10	681	1,635	15	1,022	2,554
Peru	32.17	5	1,609	4,021	10	3,217	7,721	15	4,826	12,064
Uruguay	3.46	16.4	567	1,417	16.4	567	1,361	16.4	567	1,417
Venezuela	31.98	16	5,117	12,792	16	5,117	12,280	16	5,117	12,792
Totals	**622.00**		**59,760**	**149,399**		**75,339**	**180,813**		**90,917**	**227,293**

*millions

Invasive aspergillosis

Invasive aspergillosis is frequently missed as a diagnosis, even in the best clinical units. A wide variety of patients are affected, usually at a low frequency, so clinicians have to be very alert to consider it. The chest radiograph is often negative until late in the illness and radiological features are often not distinctive. Blood cultures are always negative and respiratory cultures insensitive. The best test for diagnosis is the antigen test, but even this is often falsely negative, especially in serum in non-neutropenic patients. Undiagnosed almost all patients die, and it is the commonest missed infection in intensive care unit patients at autopsy. Treatment with voriconazole is effective in about 70% of cases.

As multiple clinical specialties see this illness occasionally and diagnosis requires more than one test, surveillance is not straightforward and expensive to undertake. Therefore, estimates of incidence are scanty. In the highest risk neutropenic hematology patients, antifungal prophylaxis is routinely given, reducing cases, if effective.

GAFFI has defined the likely burden of the most well-define risk groups with the following assumptions:

1. The risk of IA in acute myeloid leukaemia (AML) patients is 10%, probably a conservative estimate (Chen, 2018).
2. The annual incidence of AML is 4.7/100,000 in high income countries, 3.8 in those with 'medium human development', and 2.5 in those with 'low human development' (UICC, 2014).
3. The number of cases of IA in all other hematological malignancy, bone marrow failure and lymphoma cases is the same as for AML (Perkhofer, 2010; Lortholary, 2011; Chen, 2018).
4. IA in HIV is not diagnosed before death and contributes to 4% of HIV deaths.
5. IA complicates the course of 2.6% of patients with lung cancer (Yan, 2009).
6. IA occurs in 1.3-3.9% of admission to hospital of COPD patients (Guinea, 2010; Xu, 2012).
7. The prevalence of COPD GOLD stage 2-4 and annual admission proportions are drawn from several sources (Menezes, 2005; Buist, 2007; Crawford, 2012; Caballero, 2008; Jaganath, 2015; Echazarret, 2018).

Many other groups of patients are affected notably rheumatological conditions (4% risk in systemic lupus erythematosus), other cancer patients who become neutropenic or need high dose corticosteroids, medical intensive care unit patients (risk 2-5%), those with liver failure (4%) and those with severe influenza (19%), as well as transplant recipients, especially lung transplant patients. Overall the numbers affected are small, apart from ICU units where substantial numbers develop IA.

Overall therefore there are likely to be a minimum of 68,250 patients (11/100,000) in Latin America, and if the IA rate in COPD hospitalization is actually 3.9%, then a minimum of 188,000 or 30/100,000. An outbreak of severe influenza would greatly increase numbers. The low estimate for Mexico is consistent with a recent epidemiological study from 4 hospitals, scaled nationally (7,851 cases) (Corzo-Leon, 2018).

Table 5. See page 15

Table 5. Modelling for invasive aspergillosis (IA) in 4 risk groups: leukaemia and lymphoma, lung cancer, HIV and COPD.

												Lower estimate		Higher estimate	
Country	**Population 2017***	**AML cases**	**IA Leukemia**	**HIV IA Deaths**	**Lung Cancer cases**	**IA Lung Cancer**	**COPD Gold II-IV cases**	**COPD % admissions**	**COPD admissions**	**IA COPD 1.3%**	**IA COPD 3.9%**	**IA total Low**	**IA rate 100,000**	**IA total Higher**	**IA rate 100,000**
Argentina	44.27	2,081	416	68	11,595	301	3,981,760	7.0	278,723	3,623	10,870	4,409	9.96	11,656	26.33
Bolivia	11.05	276	55	24	862	22	765,066	10.0	76,507	995	2,984	1,096	9.92	3,086	27.92
Brazil	209.30	7,953	1,591	600	34,511	897	12,645,044	20.0	2,529,009	32,877	98,631	35,965	17.18	101,719	48.60
Chile	18.05	848	170	52	3,873	101	1,275,274	10.0	127,527	1,658	4,974	1,980	10.97	5,296	29.34
Colombia	49.07	1,865	373	100	5,856	152	1,351,787	14.0	189,250	2,460	7,381	3,085	6.29	8,006	16.32
Costa Rica	4.91	186	37	16	452	12	151,342	10.0	15,134	197	590	261	5.33	655	13.35
Cuba	11.48	436	87	18	6,914	180	1,659,993	10.0	165,999	2,158	6,474	2,443	21.28	6,759	58.88
Dominican Rep'	10.77	269	54	48	1,379	36	1,502,778	10.0	150,278	1,954	5,861	2,091	19.42	5,999	55.70
Ecuador	16.62	632	126	38	1,135	30	1,152,252	20.0	230,450	2,996	8,988	3,190	19.19	9,181	55.24
El Salvador	6.38	159	32	26	430	11	198,834	10.0	19,883	258	775	328	5.14	845	13.24
Guatemala	16.91	643	129	9	392	10	426,000	10.0	42,600	554	1,661	701	4.15	1,809	10.70
Honduras	9.27	232	46	22	387	10	279,992	10.0	27,999	364	1,092	442	4.77	1,170	12.63
Mexico	129.20	4,910	982	140	7,811	203	3,946,982	10.0	394,698	5,131	15,393	6,456	5.00	16,718	12.94
Nicaragua	6.22	155	31	9	322	8	190,340	10.0	19,034	247	742	296	4.76	791	12.71
Panama	4.10	193	39	24	442	11	214,713	10.0	21,471	279	837	353	8.62	911	22.23
Paraguay	6.81	259	52	25	766	20	406,136	10.0	40,614	528	1,584	625	9.17	1,681	24.67
Peru	32.17	1,222	244	40	3,210	83	565,612	13.0	73,530	956	2,868	1,324	4.12	3,236	10.06
Uruguay	3.46	162	32	12	1,574	41	250,346	10.0	25,035	325	976	411	11.88	1,062	30.71
Venezuela	31.98	1,215	243	94	4,948	129	1,795,329	10.0	179,533	2,334	7,002	2,799	8.75	7,467	23.35
Totals	**622.00**	**23,697**	**4,739**	**1,364**	**86,859**	**2,258**	**32,759,580**		**4,607,275**	**59,895**	**179,684**	**68,256**	**10.97**	**188,045**	**30.23**

*millions

Chronic pulmonary aspergillosis

Chronic pulmonary aspergillosis (previously known as aspergilloma) (CPA) is a subtle, progressive lung infection, usually following TB or complicating emphysema. Many other underlying pulmonary conditions are associated with CPA including asthma, prior pneumothorax, sarcoidosis, rheumatoid arthritis, previous lung surgery or pneumonia and non-tuberculous mycobacterial infections. It leads to serious haemoptysis, progressive lung fibrosis with dyspnea and general symptoms of fatigue and weight loss. The key diagnostic tests are CXR (or CT scan) and Aspergillus antibody in serum (Denning, 2018).

CPA is frequently mis-diagnosed as TB, although many of the radiological features are distinctive. In Latin America, chronic pulmonary histoplasmosis, coccidioidomycosis and paracoccidioidomycosis are also present, each also diagnosed partly with specific antibody tests. In one unpublished study from TB centres in Manaus, 7% of cases of possible TB were pulmonary mycoses, 67% of these were CPA.

A small number of patients can undergo surgical resection, although recurrence occurs in ~25% (Farid, 2013). About 60% of CPA cases respond to oral itraconazole therapy, with reduced symptoms, weight gain, reduced haemoptysis and no further fibrosis. Alternative therapy with voriconazole and intravenous amphotericin or echinocandin is also partially effective. The annual mortality is about 15%, with ~75% of patients dying over 5 years, unless actively treated (Lowes, 2017).

The burden of CPA is difficult to estimate because of historical difficulties in diagnosis, and multiple risk groups. A UK study from the 1960's found ~22% of patients with a cavity after pulmonary TB to have CPA, and this translated, using 2005 WHO TB data, into a global annual incidence of 372,000 and prevalence of 1.17 million (Denning, 2011). These data are based on pre-HIV TB, and now 2 studies from Africa show that the prevalence of CPA in HIV patients mirrors that in non-HIV patients (Oladele, 2017; Page, 2019). In Uganda, the annual rate of CPA development 2-7 years after successful treatment for TB was 6.5% in those with cavitation and 0.2% in those without (Page, 2019). As co-infected TB/HIV patients survive longer, the rate of CPA will rise. COPD is a common underlying disease (ie ~30%) in patients with CPA, but CPA prevalence in COPD has not been ascertained.

The estimates of CPA in Latin America are based on the following assumptions:

1. Pulmonary TB survivors are taken from WHO 2017 country statistics and assume a 10% mortality for TB.
2. After pulmonary TB, 30% are left with cavitation, and there is an annual 6.5% CPA rate in these patients and a 0.2% rate in the 70% without cavitation.
3. The annual incidence of CPA is converted to a 5 year period prevalence assuming an annual mortality of 15%.
4. TB is assumed to be the underlying pulmonary disease in 20-50% of CPA patients, depending on the annual incidence of TB in the population and prevalence of COPD. An individual country multiplier is applied to account for this.
5. COPD prevalence varies widely across the Americas and Caribbean and is an important underlying disease for CPA. The multiplier used reflects 2 factors - the TB incidence and COPD prevalence. So the total CPA prevalence is a product of the CPA after TB prevalence and the multiplier.

Based on these estimates, the prevalence of of CPA patients following TB in Latin America is about 12,400, and the overall CPA prevalence is about 33,600 (5.4/100,000). This overall figure obscures remarkable country variation most related to TB and COPD rates. There are probably high rates in Peru (Bustamante, 2018) and Bolivia (TB related), Dominican Republic (TB and COPD related) and low rates in Costa Rica, Mexico and Cuba.

Table 6. See page 17

Additional information here:
www.gaffi.org/media/fact-sheets

Table 6. Estimated prevalence of chronic pulmonary aspergillosis (CPA) based on TB annual incidence and COPD prevalence

Country	Population 2017*	TB Incidence	Pulmonary %	Pulmonary TB Survivors	Cavitation rate	TB CPA Incidence	TB CPA prevalence	COPD 100,000	CPA multiplier	CPA total	CPA 100,000
Argentina	44.27	12,000	84	9,072	0.30	190	598	899	4	2,391	5.40
Bolivia	11.05	12,000	77	8,316	0.30	174	548	692	3	1,643	14.87
Brazil	209.30	91,000	87	71,253	0.30	1,489	4,694	604	3	14,082	6.73
Chile	18.05	3,200	81	2,333	0.30	49	154	707	3	461	2.55
Colombia	49.07	16,000	83	11,952	0.30	250	787	275	2	1,575	3.21
Costa Rica	4.91	470	84	355	0.30	7	23	308	2	47	0.95
Cuba	11.48	820	88	649	0.30	14	43	1,446	6	257	2.24
Dominican Republic	10.77	4,800	88	3,802	0.30	79	250	1,395	5	1,252	11.63
Ecuador	16.62	7,200	82	5,314	0.30	111	350	693	3	1,050	6.32
El Salvador	6.38	4,600	90	3,726	0.30	78	245	312	2	491	7.70
Guatemala	16.91	4,300	94	3,638	0.30	76	240	252	2	479	2.83
Honduras	9.27	3,500	89	2,804	0.30	59	185	302	2	369	3.99
Mexico	129.20	28,000	79	19,908	0.30	416	1,311	305	2	2,623	2.03
Nicaragua	6.22	2,800	88	2,218	0.30	46	146	306	2	292	4.70
Panama	4.10	2,200	87	1,723	0.30	36	113	524	3	340	8.31
Paraguay	6.81	3,000	91	2,457	0.30	51	162	596	3	486	7.13
Peru	32.17	37,000	81	26,973	0.30	564	1,777	176	2	3,554	11.05
Uruguay	3.46	1,100	90	891	0.30	19	59	724	3	176	5.09
Venezuela	31.98	13,000	89	10,413	0.30	218	686	561	3	2,058	6.44
Totals	**622.00**	**249,007**		**187,795**		**3,925**	**12,371**			**33,626**	**5.41**

*millions

Fungal asthma (ABPA and SAFS)

Asthma is a heterogenous disorder with many different triggers, much variability in severity and remarkable variation over the course of life. The Global Burden of Disease estimates that about 450,000 people die of asthma each year, and mostly in adulthood (GAFFI Roadmap, 2015). The most problematic 10% of asthmatics consume about 70% of healthcare costs in medication, medical and nursing visits, attendance at emergency rooms and admissions to hospital.

Both environmental exposure to fungi (ie in damp buildings) and long-term fungal colonization of the airway precipitate asthma for the first time and exacerbate asthma with both attacks and persistent or poorly controlled asthma (Denning, 2014). A proportion of these patients have allergic bronchopulmonary aspergillosis (ABPA) and some have severe asthma with fungal sensitisation (SAFS). Both entities respond to oral antifungal medication (itraconazole and voriconazole, and a few to terbinafine), with response rates ~60% (Denning, 2014; Li, 2018). Better asthma control, with reduced corticosteroid use and improved quality of life are the principal benefits.

Globally about 4.8 million adults have ABPA (Denning, 2013). This assumes that ~2.5% (0.7-3.5%) of adults referred to a specialist over 1-4 years have ABPA (6 studies from Ireland, New Zealand, China, Saudi Arabia and South Africa). It could both under- and over-estimate prevalence. It is likely an under-estimate for India where this disease is more common. ABPA also occurs in children but is probably uncommon. SAFS is estimated to affect ~6.5 million adults (range 3.25-13 million) worldwide depending on the frequency of severe asthma (5-20% of all asthmatics). Again, this entity probably occurs in children too, but is poorly documented.

For Latin America, estimates for ABPA and SAFS have been made, in the absence of any epidemiology studies from the whole continent. The assumptions made are as follows:

1. Adult asthma prevalence is taken from the WHO World Health Survey in 2002-2003 by To et al (2012), Carrasco (1987) for Venezuela, and individual country burden papers published for Argentina (Riera, 2018) Chile (Alvarez Duarte, 2017), Dominican Republic (Gugnani, 2016) and Uruguay (Macedo-Vinas, 2018).
2. ABPA prevalence is assumed to be 2.5% (Denning, 2013).
3. Fungal sensitisation prevalence in severe asthma is assumed to be 33%.
4. Severe asthma affects 10% of the adult asthma population, so SAFS prevalence is estimated at 3.3% of adult asthma.
5. There is a 25% overlap between ABPA and SAFS, so the overall number of fungal asthma cases is reduced by 25%. (Fungal asthma adjusted)

The estimates above rely on old estimates of asthma prevalence for many countries. Asthma severity often increases with age up to about 70 years and often co-exists with COPD in older adults. Skin test surveys of fungal allergy are uncommon in Latin America (Twaroch, 2015) (Figure 4).

Table 7. See page 19

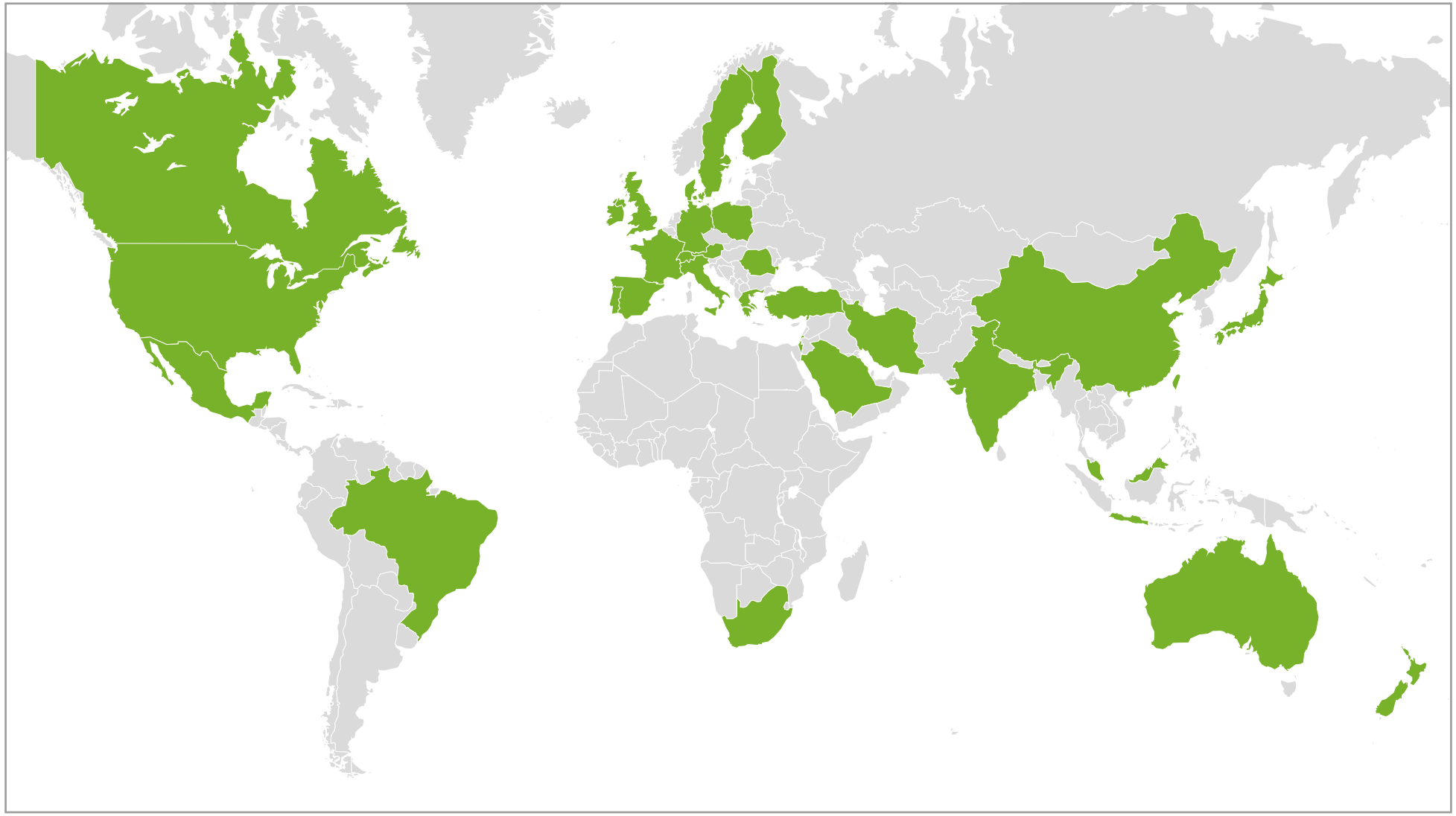
Fig 4. See page 20

Table 7. Estimates of the prevalence of ABPA and SAFS and all fungal asthma in adults in Latin America.

Country	Population 2017*	Child population	Adult population*	Adult asthma %	Adult asthma cases	ABPA cases	SAFS cases	Fungal asthma adjusted	Fungal asthma 100,000
Argentina	44.27	25%	33.20	13.94	4,628,429	115,711	152,738	201,337	455
Bolivia	11.05	36%	7.07	2.13	150,634	3,766	4,971	6,553	59
Brazil	209.30	25%	156.98	12.94	20,312,565	507,814	670,315	883,597	422
Chile	18.05	23%	13.90	5.00	694,925	17,373	22,933	30,229	167
Colombia	49.07	33%	32.88	6.33	2,081,108	52,028	68,677	90,528	184
Costa Rica	4.91	24%	3.73	2.39	89,113	2,228	2,941	3,876	79
Cuba	11.48	17%	9.51	9.97	947,692	23,692	31,274	41,225	359
Dominican Republic	10.77	31%	7.43	9.97	740,901	18,523	24,450	32,229	299
Ecuador	16.62	29%	11.88	2.13	253,114	6,328	8,353	11,010	66
El Salvador	6.38	32%	4.33	2.42	104,802	2,620	3,458	4,559	71
Guatemala	16.91	40%	10.15	2.42	245,533	6,138	8,103	10,681	63
Honduras	9.27	32%	6.26	2.42	151,568	3,789	5,002	6,593	71
Mexico	129.20	29%	91.73	2.39	2,192,395	54,810	72,349	95,369	74
Nicaragua	6.22	35%	4.07	2.42	98,562	2,464	3,253	4,287	69
Panama	4.10	26%	3.03	2.42	73,306	1,833	2,419	3,189	78
Paraguay	6.81	30%	4.77	6.40	305,133	7,628	10,069	13,273	195
Peru	32.17	28%	23.16	6.40	1,482,394	37,060	48,919	64,484	200
Uruguay	3.46	22%	2.70	10	269,646	6,741	8,898	11,730	339
Venezuela	31.98	29%	22.71	6.40	1,453,171	36,329	47,955	63,213	198
Totals	**622.00**		**449.48**		**36,274,989**	**906,875**	**1,197,075**	**1,577,962**	

*millions

Figure 4. Countries where allergy skin testing had been done and published up to 2014 (Twaroch, 2015).



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