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The Burden of Diseases Caused by Invasive Fungal Infections

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Abstract:
Invasive Fungal Infections (IFIs) have increasingly become a concern in many parts of the world. Challenges around early and effective diagnostics as well as shifting demographic characteristics are among the critical factors driving the increasing threat of IFIs. The aim of the current study was to estimate the burden of three main IFIs—*Candida* infections, *Aspergillus* infections, and Mucormycosis—in Saudi Arabia. Data were collected from published government records, research studies directly focusing on these diseases in Saudi Arabia, and expert advice from healthcare professionals where some data were completely unavailable to guide the estimation of the burden of disease. Findings showed that with a total population of slightly above 32 million according to the government records of 2022, Saudi Arabia's major burden of the investigated IFIs is associated with *Candida* infections. Among 1,568 cases appearing in records used in this study to inform the burden of disease for *Candida* infections, it was determined that four main strains exist, *Candida Albicans*, *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis*, and *Candida krusei*. *C. Albicans* presents the highest burden owing to the many cases (40.11%, n = 629) that emerged from the total cases reported in all cases. *Aspergillus* emerged as the second most burdening IFI, with an estimated burden of about 2,445 cases per year, and with the *Aspergillus flavu* being the most prevalent strain in Saudi Arabia. Mucormycosis was not a major threat, with the estimated burden of disease being 109 cases per year for the entire population. Other IFIs reported in the data records were cryptococcal meningitis, gastrointestinal basidiobolomycosis, and brain abscesses, but none of these presented any significant burden. The findings show that the highest burden of IFIs in Saudi Arabia is due to *Candida* infections and particularly the *C. Albicans* strain, with *Aspergillus* coming closely as the second most burdening condition. Accordingly, in healthcare planning and resource allocation to address IFIs, there is need for the government and other relevant stakeholders to focus on enhancing resources for the diagnosis and treatment of cases of *Candida* and *Aspergillus* infections, as these represent the most significant burden.

KEYWORDS: Invasive, Fungal, Infections, Saudi Arabia, Burden, Candida infections, Aspergillus infections, Mucormycosis

Introduction

Invasive fungal infections are increasingly recognized as a significant global health concern, particularly in areas with expanding immune-compromised populations due to various medical conditions like HIV/AIDS, cancer treatments, organ transplants, and prolonged hospital stays [1-4]. In contrast to superficial fungal infections, IFIs result from systematic yeasts or molds which attack deep-seated body tissues, posing significant threats to public health due to their high morbidity and mortality rates [1]. IFIs, which are caused by fungi such as *Candida*, *Aspergillus*, *Cryptococcus*, and *Mucorales*, can result in severe illness and death if not treated promptly [5, 6]. Clinically, IFIs manifest in various forms, ranging from colonization in allergic bronchopulmonary disease to other forms such as actively infecting local aetiologic agents [5]. Recently, the world faced challenges due to the COVID-19 pandemic, during which three fungal pathogens associated with IFIs—*Aspergillus*, *Candida*, and Mucorales—were shown to cause co-infections in COVID-19 patients, highlighting the severity of these infections [7-10]. The burden of invasive fungal infections in Saudi Arabia is becoming more pronounced due to the country's unique population dynamics, healthcare advancements, and increasing prevalence of chronic diseases, all of which warrant research into the epidemiology of these conditions and an accurate assessment of their impact on both the government and the broader public [11-13]. According to Khateb et al., there are clear indicators of an increase in fungal infections across the Kingdom of Saudi Arabia [11]. Research shows that over the short period between 2013 and 2019, there was a significant increase in reported fungal occurrences in Saudi Arabia, with *C. parapsilosis* being reported as the leading cause [11].

Due to the strong commitment of the Saudi Arabian government and in accordance with the Vision 2030 healthcare goals, the healthcare system in Saudi Arabia has seen rapid modernization, leading to improved survival rates for patients with compromised immunity, including organ transplant recipients and individuals undergoing chemotherapy [14-17]. While these advancements are commendable, they also contribute to the increased risk of opportunistic infections like IFIs. The arid climate of Saudi Arabia, which fosters the growth of certain fungi, coupled with increased urbanization and construction activity, has significantly elevated the prevalence of fungi capable of causing infections in vulnerable individuals [18].

The epidemiology of IFIs in Saudi Arabia is complex, according to recent research findings. Such complexity arises from a variety of factors, including geographic variation, patient demographics, and healthcare settings [11, 19]. Recent studies further indicate that invasive candidiasis and aspergillosis are the most common types of IFIs in Saudi Arabia, mirroring global trends [20-22]. However, localized outbreaks of rarer fungal infections, such as mucormycosis, have been reported, particularly in patients with uncontrolled diabetes, which is prevalent in the country. Recent research indicates that with a prevalence of

23.9%, Saudi Arabia ranks among the top ten nations globally for diabetes prevalence [23-28]. Given the strong correlation across IFIs, an understanding the risk of these infections is crucial for developing targeted prevention and treatment strategies [29].

The burden of disease caused by IFIs is considerable, impacting both morbidity and mortality as well as imposing a substantial economic strain on healthcare resources. With the current literature indicating that these infections are increasingly becoming a global concern, thorough research is essential to understand the specific burden they impose on national and global healthcare resources in an effort to mitigate them and minimize the risks that IFIs present, particularly to vulnerable populations [30]. The burden of disease in Saudi Arabia is potentially impacted by many factors and made more complex by delayed diagnoses and limited access to antifungal therapies in some regions of the country [31]. The focus of this study was to explore the burden of invasive fungal infections in Saudi Arabia and assess their impact on the population and healthcare system, specifically on *Candida* infections, *Aspergillus* infections, and Mucormycosis.

Methods: The total population of Saudi Arabia was estimated using data from the National Statistics 2022 Census. These data were the most realistic for use in this study for population estimations as they were the most recent publicly available data. The estimations here were for the following invasive fungal infections: *Candida* infection (IC), *Aspergillus* infection (IA), Mucormycosis, and other Invasive Fungal Infections (IFI) diseases. Information on incidences was obtained from different sources, including studies published specifically on these diseases or a combination of them, the global burden of disease website, and government reports on healthcare updates. It is important to note that information on invasive fungal infections across Saudi Arabia is scarce, potentially due to limited research in this area. In instances where no information was available, expert advice from healthcare professionals in hospitals with documented IFI cases was sought.
Ethical approval for this study was not necessary as it did not involve any human participants. In cases where expert advice on data was requested, the information sought was only quantitative with no need for patient personal information in order to estimate of burden of disease in this study.
In some cases, there were multiple published studies on a particular IFI condition relevant to this study. In these cases, all data were presented in table format to convey the comprehensive burden that these diseases present to the Saudi Arabian government and the wider public in terms of healthcare resources allocation. The following specific approaches were adopted to gather the data for each IFI condition covered in this study.
Candida Infection
Infectious candidiasis is among the most prevalent IFIs studied globally, including in Saudi Arabia. The current study found several published and credible sources

that informed the estimates for this IFI across the Saudi Arabian population. All sources used for this IFI had information on all variants of *Candida* infection from *C. albicans, C. tropicalis, C. grabrata,* and *C. parapsilosis* to *C. krusei* [32-37]. From the data presented in the sources, an estimation for each variant was calculated by computing the mean and percentage proportions for the different variants.

Aspergillus Infection

While studies were available for *Candida* than *Aspergillus*, several credible published sources informed this study's estimate of the disease burden in Saudi Arabia. Information in these records was mixed with some findings reporting only the prevalence rate of *Aspergillus* infection across the Saudi Arabian population, while others included further details which included specific variants of the IFI [13, 38-39].

Mucormycosis

There was scarcity of published records providing information necessary for quantifying the disease burden related to Mucormycosis, another critical IFI that, if not promptly addressed for effective diagnosis and treatment, can lead to serious health complications. In addition, professional expertise was sought from healthcare experts in several hospitals across Saudi Arabia to ensure that the information presented in this study is optimally credible and reliable.

Other IFIs

Similar to Mucormycosis, there was a dearth of information on other IFIs that could have contributed to a more comprehensive understanding of the disease burden to Saudi Arabia as a result of IFIs. However, when reviewing relevant sources, three records were identified that proved useful, alongside additional information gathered from expert advice, in determining the burden of disease of IFIs in Saudi Arabia.

Results

The population of Saudi Arabia, according to the Saudi Census portal, was 32,175,224 as of 2022 [35]. The predominant demographic was males, representing a total of 61.1% (n = 19,678,595). The elderly (i.e., individuals aged 65 years and above) and those considered to be a high risk population for IFIs due to possibility of co-morbidity of conditions such as diabetes and others represented approximately 2.6% of the total population. Table 1 captures further details about the demographic of the Saudi population.

Table 1: KSA Total Population and Distribution

Region	Total	Children	Middle Age				Elderly
		0-14 years	15-19 years	20-24 years	25-54 years	55-64 years	65+ years
Ar Riyadh	8,591,748	1,900,312	518,741	707,940	4,838,516	435,109	191,130
Makkah Al Mukarramah	8,021,463	1,833,290	547,028	641,718	4,270,773	475,677	252,977
Eastern Region	5,125,254	1,213,128	305,980	384,352	2,862,215	252,256	107,323
Al Madinah	2,137,983	571,538	159,653	177,408	1,061,207	105,847	62,330
Aseer	2,024,285	549,125	163,425	167,879	979,864	95,480	68,512
Jazan	1,404,997	410,091	122,685	122,332	633,440	65,409	51,040
Al Qaseem	1,336,179	347,478	103,451	121,814	662,150	65,249	36,037
Tabuk	886,036	255,569	70,217	75,551	428,694	36,397	19,608
Hail	746,406	205,033	55,631	62,189	366,797	34,510	22,246
Al Jawf	595,822	202,863	46,548	47,901	262,981	23,124	12,405
Najran	592,300	185,587	45,838	49,022	275,348	21,636	14,869
Northern Borders	373,577	119,552	29,422	31,039	170,923	13,812	8,829
Al Bahah	339,174	93,324	28,081	26,837	158,024	18,365	14,543
Total	32,175,224	7,886,890	2,196,700	2,615,982	16,970,932	1,642,871	861,849

The proportional distribution of the population across all 13 regions is presented in the pie chart.

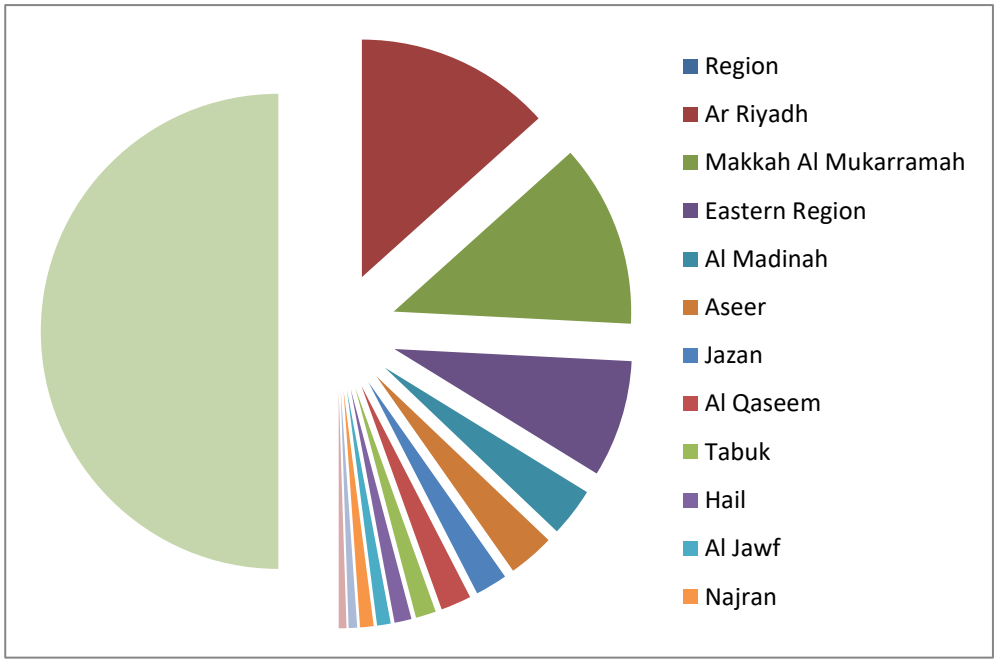

Figure 1: Regional Population Distribution

Candida Infection

An analysis of the data indicated that among of all the variants of *Candida* invasive infections, *C. albicans* accounts for the highest disease burden, averaging 40.11% (*n* = 629) of all cases (*N* = 1568) documented in the records informing this study on this particular strain of Candida infections. The data revealed a prevalence rate of 1.546 per 1,000 patients for any variant of *Candida* infection. Data from the reviewed records indicated that in one case involving 652 invasive *Candida* infections (ICI), *C. albicans* was the most common IFI, representing 38.7% of all cases [32]. In comparison, of the 652 ICI cases used in this study, a total of 123 (18.9%) cases were for *C. tropicalis* with the remainder being distributed among *C. glabrata* (16.3%, *n* = 82), *C. parapsilosis* (12.6%, *n* = 82), and *C. krusei* (1.4%, *n* = 9) [32].

In another study involving 252 invasive *Candida* infections, *C. albicans* emerged again as the most common IFI with a proportion of 34.1% (*n* = 86). The other variants were distributed as follows: *C. tropicalis* (15.5%, *n* = 39), *C. glabrata* (9.1%, *n* = 23), *C. parapsilosis* (11.9%, *n* = 30), and *C. krusei* (4.0%, *n* = 10) [33]. The third record that informed this study on the burden of invasive *Candida* infections showed that total isolates were 98 and the distribution was: *C. albicans* (53.0%, *n* = 52), *C. tropicalis* (18.4%, *n* = 18), *C. glabrata* (7.1%, *n* = 7), *C. parapsilosis* (15.9%, *n* = 16), and *C. krusei* (5.1%, *n* = 5) [34]. The next set of data involved a total of 294 isolates for invasive *Candida* infections, and the distribution was: *C. albicans* (50.7%, *n* = 149), *C. tropicalis* (20.7%, *n* = 61), *C. glabrata* (7.1%, *n* = 21), *C. parapsilosis* (10.9%, *n* = 32), and *C. krusei* (7.8%, *n* = 23) [35]. In yet another record, a total of 189 isolates were examined for the distribution of invasive *Candida* infections, revealing the variants of *Candida* were as follows: *C. albicans* (50.3%, *n* = 95), *C. tropicalis* (27.0%, *n* = 51), *C. glabrata* (7.4%, *n* = 14), *C. parapsilosis* (7.9%, *n* = 15), and *C. krusei* (3.2%, *n* = 6) [36]. In a final published source of the total isolates for ICI, the distribution of the various variants of *Candida* was investigated using 83 isolates and the findings showed that of these, the proportions were: *C. albicans* (46.0%, *n* = 38), *C. tropicalis* (10.8%, *n* = 9), *C. glabrata* (4.8%, *n* = 4), *C. parapsilosis* (10.8%, *n* = 9), and *C. krusei* (6.0%, *n* = 5) [37].

Aspergillus Infection

The investigation into *Aspergillus* infections showed that data on this particular IFI are scarce. In the available data records, it emerged that *Aspergillus* infection in Saudi Arabia has a rate of 7.6 per 100,000 persons, indicating a prevalence rate of 0.0076 % for the entire population, or a burden of 2,445 per year based on the 2022 census data (Table 1) [39]. In another data record, the prevalence of *A. fumigatus, A. niger, A. flatus*, and others were shown to have a prevalence of 60% (*A. fumigates*), 10% (*A. niger*), 10% (*A. flatus*), and 20% for the other unknown variants combined [13]. In another study, the *Aspergillus flatus* was shown to be the most prominent variant [38]. Finally, an additional record showed that among 250 isolates of *Aspergillus* infection, 45.6% (*n* = 114) were of the *A. niger* variant, 39.2% were of the *A. flatus* variant, 9.2% were of the *A. fumigates* variant, and 6% (*n* = 15) were of the *A. terreus* variant [39].

Mucormycosis

Data for this particular IFI were scarce, and from the available records it was established that the prevalence rate of mucormycosis in Saudi Arabia is 0.0034 per 100,000 persons (0.0000034%), equivalent to a burden of 109 cases per year when extended to cover the entire Saudi population according to the 2022 census data [40].

Other Invasive Fungal Infections

In addition to the main fungal infections, there were also notable incidences of other IFIs. There were no records of cryptococcal meningitis, but one record showed that some cases of the rare gastrointestinal basidiobolomycosis have been reported in Saudi Arabia [41]. However, the information from this record was not specific enough to allow for any quantification of the burden presented by gastrointestinal basidiobolomycosis in Saudi Arabia. Similar incidences of inconclusive data to quantify the burden of disease in KSA were reported for brain abscesses [42-43].

Discussion

This study estimated the burden of invasive fungal infections (IFIs) in Saudi Arabia with a specific focus on *Candida* infections, *Aspergillus* infections, and Mucormycosis for the purpose of highlighting the growing concern regarding these infections in an immunocompromised population. The findings reflect the global trend of IFIs where Candida and Aspergillus infections dominate the epidemiological landscape, but with notable regional characteristics driven by Saudi Arabia's unique healthcare and environmental context [32-37]. The prevalence of *C. albicans* as the most common strain in Saudi Arabia aligns with international studies which point to its predominance in IFI cases [13, 32]. The high incidence of *Candida* infections, particularly in critical care settings and among patients with prolonged hospital stays or undergoing invasive procedures, significantly emphasizes the need for targeted infection control strategies in healthcare facilities across Saudi Arabia. Despite *Candida albicans* being the leading threat to Saudi Arabia's healthcare system in relation to the studied IFIs, it is critical to note that the increasing rates of *C. tropicalis* and *C. glabrata* also signal potential changes in the epidemiological patterns of IFIs that require further study, particularly regarding antifungal resistance, which has been rising globally.

Aspergillus was also identified as a significant contributor to IFI-related morbidity in Saudi Arabia. This finding is supported by literature that indicates that this fungal pathogen thrives in arid climates, and its prevalence in Saudi Arabia is further worsened by factors such as construction and urbanization, which promote the spread of spores [3]. The scarcity of detailed research on Aspergillosis in Saudi Arabia, however, poses a challenge in developing a comprehensive response; this points to the need for more robust epidemiological surveillance. The rare but deadly Mucormycosis also emerged as a concern, especially among individuals with uncontrolled diabetes—a demographic particularly prominent in Saudi Arabia due to the high national prevalence of diabetes (23.9%). Mucormycosis has severe outcomes due to delayed diagnosis and limited

treatment options. The scarcity of data on this infection suggests an urgent need for improved diagnostic capabilities and awareness, particularly in regions with a high diabetic population.

Conclusion

This study highlights the growing burden of invasive fungal infections in Saudi Arabia, with *Candida* and *Aspergillus* infections identified as the primary etiological agents. The arid climate, rapid urbanization, and increasing population of immunocompromised individuals in the Saudi Arabia contribute to the complexity of IFI epidemiology. Furthermore, the study underscores the need for more comprehensive data, particularly regarding rare fungal infections like mucormycosis, which disproportionately affect vulnerable populations such as diabetic patients. Addressing the challenges posed by IFIs in Saudi Arabia will require enhanced diagnostic capacities, better infection control measures, and the development of targeted therapeutic strategies. Through prioritizing fungal infection research and public health interventions, Saudi Arabia can mitigate the morbidity, mortality, and economic costs associated with these life-threatening infections. As the country continues to advance its healthcare systems, it is crucial to incorporate robust strategies for the prevention and management of IFIs to safeguard the most vulnerable populations.

Declarations

Ethical Approval: Ethical approval to conduct the research was issued from Taif University. The study was conducted in accordance with the Declaration of Helsinki.

Author Contributions: The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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Informed Consent Statement: The study did not use human participants, and there was no need for informed consent.

Data Availability Statement: All data in this study are included in this manuscript.

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Conflicts of Interest: I certify that I have no conflict of interest. I further certify that no other relationship, bias, or ethical conflict exists in this article.

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