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Review Article

A COMPREHENSIVE OVERVIEW ON MANAGEMENT OF FUNGAL DISEASE BY VACCINES, DRAWBACKS, AND CHALLENGES

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ABSTRACT

Infections caused by fungi are a large and varied category of diseases that impact all living things on Earth. Underscoring their worldwide epidemiological effect, this review focusses on the categorization, pathogenic processes, and clinical symptoms of superficial and systemic mycoses. Morphological traits, virulence factors, and environmental adaptations that allow survival and infection are examined in relation to several fungal taxa. New opportunistic fungi and the rise of resistant strains are other topics of discussion. Antifungals and fungal vaccine and diagnostic methods are in the review. In order to better diagnose, prevent, and manage mycotic infections, it is essential to understand the biology and pathogenicity of fungi. This document also summarizes current research in medical mycology and suggests areas for future study to control fungal illnesses and to reduce their economic and health impacts.

Keywords: Antifungal Agents, Antifungal Resistance, Fungal Diseases, Fungal Pathogenesis, Medical Mycology, Mycoses, Opportunistic Fungi, Vaccine Development.

1. INTRODUCTION

Fungi are heterotrophs, namely, they obtain their food, energy, and carbon from dead organic matter. There are three types of fungi based on the source of nutrients: biotrophs, saprotrophs and necrotrophs. The fungi that obtain their nutrition from living organisms (plants or animals) are called biotrophs, such as rust fungi. However, the fungi that get their food from dead organisms (dead plant and animal material) are called saprotrophs, several mushrooms, mold and yeast are saprotrophs. Also, the fungi that obtain their nutrition by infecting living organisms are called necrotrophs, such as *Alternara*, *Sclerotinia sclerotiorum*. Fungi are eukaryotic organisms with a nucleus and organelles bounded to the membrane. Fungi have two parts in their structure: vegetative and reproductive. The vegetative part of fungi is called the thallus, which can be unicellular (having one cell), such as yeast, and multicellular (having two or more cells), such as mushrooms. Multicellular fungi produce microscopic tubular cells or thread-like structures in their thallus called hyphae (singular hypha). Most hyphae are separated by cells called septa (singular septum) (Kosal *et al*., 2023). Hyphae also produce spores that grow into new fungi and spread easily through the soil. Fungal agents infect host and get entry into the body of the host, develop into hyphae. Fungi are ubiquitous in the environment, and most of these are harmless. However, some fungi can cause diseases. Fungi infect humans and cause diseases by their virulence factors, especially in the immunocompromised individuals. The pathogenic fungi have specific virulent factors causing disease. Virulence factors can be divided into two categories; structural components of fungal cell wall are chitin, β-glucans, mannans, and glycoproteins unlike many bacteria fungi generally do not possess flagella. In addition, pilli are bacterial structures and not present in fungi and functional components such as enzymes, toxins, and proteins produced by fungi.

2. FUNGAL DISEASES

Fungal diseases have major impact not only on human and animal health, but also affect economic status. Fungal diseases can be in the form of mycoses or mycotoxicosis.

Mycoses:

Diseases caused by fungi are called mycoses (Kobayashi, 2001). Some of them are contagious, while others are non-contagious and can easily be transmitted through both direct and indirect interactions. In mycoses, whole pathogenic fungal organism is involved in causing disease through the processes of replication, production of toxic metabolites and severe immune responses.

Toxin mediated disease without fungal invasion:

Among toxin mediated fungal diseases, the most important is mycotoxicosis, which is a type of intoxication.

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Mycotoxicosis:

Mycotoxicosis is mainly caused by the ingestion of pre-formed mycotoxins. However, inhalation and dermal inoculation are rarely reported. Mycotoxins are secondary metabolites and common contaminants of food. Usually, these mycotoxins are present in the food materials as contaminants, especially food items based on crops such as grains, legumes, and nuts. When these mycotoxins contaminated food items are consumed by humans, these can have negative effects (Rayens *et al*., 2022). The mycotoxin ingestion leads to intoxication. According to the Food and Agriculture Organization (FAO), in 1985, 25% of the total food produced worldwide was contaminated by mycotoxins. The true prevalence of detectable mycotoxins in food crops at a global level is much higher, typically estimated at around 60% to 80%, depending on the toxin and analytical thresholds used. This higher range reflects improvements in detection methods and broader survey coverage, suggesting that mycotoxin contamination is far more widespread than the outdated 25% estimate implies, according to recent thorough reviews of mycotoxin occurrence data from global surveys, including millions of analyses of cereals and nuts (Al-Janabi *et al*., 2020). There are three main genera which produce mycotoxins. *Aspergillus*, *Fusarium* and *Penicillium* among which *Aspergillus* genus is of great importance. From this genera, *Aspergillus flavus* produces aflatoxins which cause hepatotoxicity, hepatocellular carcinoma, immunosuppression, Reyes syndrome and effect on reproduction (Alhaddad, 2022).

3. CLACIFICATION OF FUNGAL DISEASES BASED ON THE LOCATION OF SITE

Fungal diseases are also called fungal infections. Based on the site of infection, fungal diseases are classified as:

1. Superficial fungal infections
2. Cutaneous fungal infections
3. Subcutaneous fungal infections
4. Systemic fungal infections

Superficial Fungal Infection:

Superficial fungal infections or superficial mycoses are impurities that affect the outermost layers of the body, usually the skin, hair, or nails, as well as mucous membranes (Sharma *et al*., 2021). These are generally less severe than systemic infections, though these can still cause discomfort and complications if left untreated (Gupta *et al*., 2020). Superficial fungal infections are caused by fungi known as dermatophytes, non-dermatophyte moulds, yeasts, yeasts like fungi, and *Malassezia furfur* (Cunha *et al*., 2021) meanwhile mycoses are also called dermatophytosis. Dermatophytes are opportunistic infectious agents that infect the skin, hair and nails. The virulence factors of dermatophytes are keratinase enzyme that digests keratin and acidic metabolites for inducing itching. Most species are keratinophilic (have keratin), parasitic or saprophytic, that is, these infect animals and humans (Rajasingham *et al*., 2017).

There are some main superficial mycoses. The first one is tinea versicolor which is caused by three fungi named *M. globosa*, *M. furfur* and *M. sympodialis*. In this infection hyper pigmented patches appear on the skin (Cunha *et al*., 2021). The second one is white piedra which is also known as trichomycosis nodularis or trichomycosis nodosa. This is primarily a hair shaft infection which is caused by fungus *Trichosporon asahii*. Some other examples of superficial infections are *Tinea pedra*, *Tinea nigra* (Jain *et al*., 2019).

Detailed Description of Tinea Nigra:

The word "Tinea" is related to skin. It is utilized for skin infections that occur due to fungus. The word "Nigra" is taken from Negro, which means black color. Tinea nigra is a rare superficial infection that affect only upper layers of skin (epidermis and stratum corneum). In this condition, black or brown colored lesions are formed, and they primarily affect the soles of feet and palms of hands (Martínez-Ortega *et al*., 2024). The causative agent of this infection is *Hortaea werneckii* (Kelarestaghi *et al*., 2022). The black yeast *Hortaea werneckii* was isolated from Mediterranean Sea. It is also known as salt tolerant eukaryotic organism (De Leo *et al*., 2018) because it prefers hyper saline environment. For example, the Dead Sea, 3-30% of salt concentration is optimal for the growth of these fungi. *H. werneckii* is a saprophytic fungus, mostly present in soil and dead organic matter. In human body, at the temperature of 37°C these are prevalent in yeast form. So, spores are infecting form, but disease is caused by the yeast. The virulence factors of *Tinea nigra* includes breakdown are lipase as well as Keratinase. *Tinea nigra* does not produce any fluorescence. The organism targets melanocytes and an increase in their size can lead to higher melanin production, resulting in hyperpigmentation.

Cutaneous Fungal Infections:

Cutaneous fungal infections are a kind of infection which infect skin, involving its layers (epidermis, dermis, and sometimes the subcutaneous tissue) and skin related structures, including the hair and nails and causes inflammation and itching. These infections produce lesions on the aforementioned structures, which can often be painful. The severity of cutaneous fungal infections ranges from mild and superficial to severe and life-threatening (Bongomin *et al*., 2017). Dermatophytes, a class of fungus that break down keratine. Dermatophyre fungi belong to *Trichophyton*, *Microsporum*, and *Epidermophyton*. These fungi can infiltrate keratinized tissues and endure on the host surface because these have virulent factors like keratinases and other proteolytic enzymes. The most important example of cutaneous fungal infection is Tenia pedis, which is commonly referred to as athletes' foot. Other examples are tinea capitis (infection of the scalp) and tinea corporis (body ringworm). Tinea pedis is one of the dermatophytic infections that are most reported globally (Chowdhary, Sharma & Meis, 2022).

Subcutaneous Fungal Infections:

Subcutaneous fungal infections or subcutaneous mycoses are that type of infection in which the fungi deeply penetrate (Fathur Rachman, 2020) in the skin and subcutaneous tissue (Freitas *et al*., 2020). In today's times subcutaneous fungal infections are that type of conditions which are identified as neglected tropical diseases (NTDs) or skin NTDs. A vast variety of antifungal agents are available including antifungal drugs named as griseofulvin, topical azole antifungals, itraconazole, fluconazole and the allylamine, terbinafine (Hay, 2024). The three main and important classes of subcutaneous fungal infections are Sporotrichosis, Chromoblastomycosis and Mycetoma (La Hoz & Baddley, 2012).

Sporotrichosis:

The sporotrichosis is often known as rose gardener's disease, a persistent subcutaneous fungal infection (Yeo *et al*., 2023) which is caused by dimorphic fungus, *Sporothrix schenckii* (Mahajan, 2021). Spores are present in soil and vegetation, and they are also associated with plants such as rose plants. The transmission route of the spores of this fungus is wound skin. Disease starts from papule/blisters formation on skin and then cells accumulate for nodules formation, when they lead to ulcerative lesions. Sporotrichosis rate is higher in males as males are at higher risk of exposure in the fields. It affects both plants and animals. A total of 3.000 cases of animals and 2.000 cases of humans have been reported (Barros *et al*., 2011). Sporotrichosis typically results in serious skin infections. Less frequently, it might result in lung or eye infections. Transmission of fungal spores results in papule/blisters formation followed by nodular and ulcerative lesions (Mahajan, 2014). The drug of choice for sporotrichosis are itraconazole and amphotericin B medicine (Tang *et al*., 2023).

Chromoblastomycosis:

Chromoblastomycosis is chronic subcutaneous fungal infection (Baveja *et al*., 2021) that infects the skin and subcutaneous tissue caused by dematiaceous fungi (Rimet Borges *et al*., 2022), belonging to herportrichiellaceae family. Fungal apores are prevalent in soil, woods, and plants. The main causative agents of chromoblastomycosis are *Fonsecaea pedrosi*, *Fosecaea compacta*, and *Phialophora verrucose* (Abza & Babeta, 2023). Usually, infection results from the traumatic implantation of fungal elements into the skin, which is frequently caused by thorns, splinters, or small wounds sustained during outdoor or agricultural activities. In this disease there is a slow development of wart-like/ nodular lesions, typically on the hands, feet, or lower limbs. Treatment usually entails long-term antifungal therapy, which frequently uses medications like terbinafine or itraconazole. In certain situations, surgical excision, cryotherapy, or heat therapy may be necessary to manage or eradicate the lesions.

Mycetoma:

Mycetoma is caused by fungus named Eumycetes (also called eumycetoma). Mycetoma is chronic, progressively destructive and granulomatous subcutaneous fungal infection. If treatment is delayed, it may extend to the muscles and bones. The illness is typically identified by swelling of the afflicted area, formation of sinus tracts, and discharge of tiny grains harboring microorganisms. It is either caused by filamentous bacteria (actinomycetoma) or specific fungi (eumycetoma). Small cuts, punctures, or skin injuries allow the pathogenic organisms found in soil, plant materials, or thorns to enter the body and cause infection. Because of this, illness is more common in outdoor workers, such as farmers and agricultural laborers, particularly those who go barefoot. The "mycetoma belt," which includes portions of Africa, the Middle East, South Asia, and Latin America, is where mycetoma, a neglected tropical illness, is most frequently documented. The kind of organism causing the infection determines how mycetoma should be treated. While eumycetoma necessitates long-term treatment with antifungal drugs like itraconazole, actinomycetoma is typically managed with prolonged antibiotic therapy. To control the infection and stop additional harm, surgical excision of infected tissue may be required in more advanced cases.In this fungal organism produces large masses which are called grains (Ahmed & De Hoog, 2011).

Systemic Fungal Infection:

Systemic fungal infections (also known as systemic mycoses) are internal infections that occur deep within the body (Hay, 2024). Systemic fungal infections are life threatening and can also affect the skin and sometimes result in bloodstream dissemination. These infections are caused by fungi which is called endemic fungi. Soil-dwelling fungi are typically causing systemic mycoses. These infections usually start in the lungs through the inhalation of spores and then spread to other body tissues. For the treatment of systemic fungal infections voriconazole, amphotericin B or echinocandin drugs are used (Hay, 2024).

The main systemic fungal infections include

1. Histoplasmosis
2. Blastomycosis
3. Coccidioidomycosis
4. Aspergillosis

Histoplasmosis:

One kind of fungal infection that affects the lungs is histoplasmosis. It is contracted by inhaling the fungus *Histoplasma capsulatum* (Pury *et al*., 2023). In many countries, including the United States, the fungus is found in the soil that contains bat or bird droppings. Oral itraconazole therapy may be necessary for mild cases, or these may be resolved on their own. Preventive methods include limiting exposure, particularly for those at higher risk, to areas with high concentrations of fungal spores, such as caves and old buildings that contain bird droppings.

Blastomycosis:

Blastomycosis is caused by dimorphic fungus *Blastomyces dermatitidis*, hence, a life-threatening infection (Merkhofer *et al*., 2019). This is prevalent in soil and decomposing organic waste, especially in damp areas like woods and riverbanks, as the source of the fungal infection known as blastomycosis. When fungal spores are disturbed, these can fly into the air and cause infection by inhalation. The illness mostly affects the lungs, resulting in symptoms that are like pneumonia (Proia, 2010) including fever, cough, chest pain, and exhaustion (Fig 1). North America has a higher prevalence of blastomycosis, especially in the areas surrounding the Great Lakes and the Ohio and Mississippi River valleys (Benedict *et al*., 2012). Blastomycosis is treated with antifungal drugs such itraconazole or, in more extreme situations, amphotericin B (Proia, 2010).

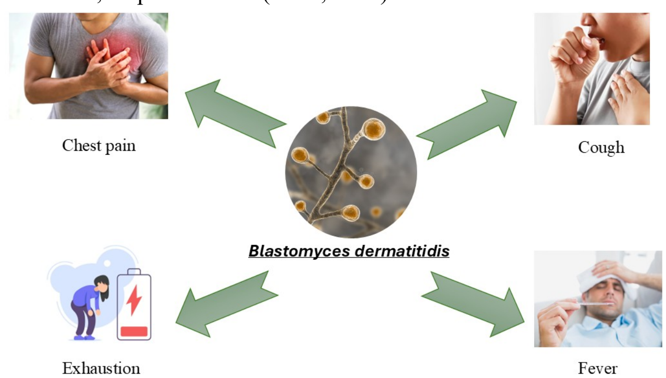

Figure 1: Symptoms of Blastomycosis (Created using Power point)

Coccidioidomycosis:

Coccidioidomycosis is commonly referred to as Valley fever and causative agent of Coccidioidomycosis is *Coccidioides posadasii* (Cai *et al*., 2022). These fungi flourish in arid and semi-arid environments. Coccidioides species, primarily *Coccidioides immitis* and *Coccidioides posadasii*, are the cause of coccidioidomycosis, a systemic fungal illness. When individuals breathe in airborne arthroconidia (spores) discharged from contaminated soil, these become infected. The fungus mostly affects the lungs after inhalation, where it can result in symptoms including fever, cough, chest pain, exhaustion, and other indicators of pneumonia. The infection usually stays confined to the lungs, but in certain people it can spread to the skin, bones, and central nervous system, which could result in dangerous side effects like meningitis. The disease is most prevalent in arid and semi-arid areas, especially in parts of Mexico, Central America, and South America, as well as the southwestern United States. Pregnant women, older people, immunocompromised persons, and those with existing medical issues are among the populations who are more susceptible to severe illness. While amphotericin B is only used for severe or life-threatening infections, more severe or widespread instances typically require antifungal therapy, typically with azole medications like fluconazole or itraconazole. Mild infections may go away on their own.

Aspergillosis:

Aspergilli are the main causative agents of aspergillosis, another opportunistic mycosis (Al-Janabi & Ali, 2020). People who have cancer (Singh, 2024) or other crippling lung conditions are susceptible to this illness. It can manifest as allergic reactions, chronic lung infections or invasive aspergillosis. The invasive form is particularly lethal, leading to severe lung damage and spreading to other organs in immunocompromised individuals. Different categories of skin fungal infections are shown in figure 2.

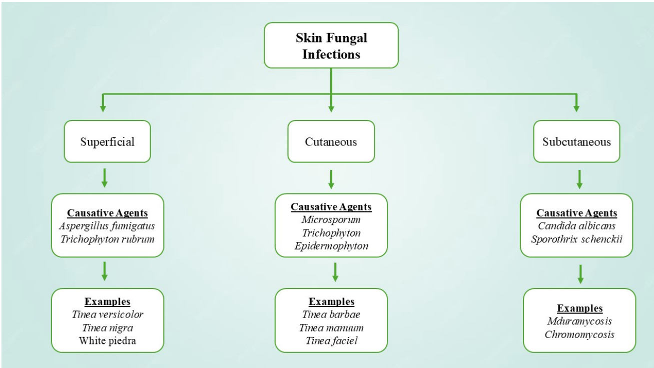

Figure 2: Categories of skin fungal infections (Garg *et al*., 2020)

4. EPIDEMIOLOGY OF FUNGAL INFECTIONS

Although fungi act as major pathogens of plants, insects, amphibians, and reptiles, they rarely infect mammals. However, in recent decades, a significant increase in the burden of fungal disease has been observed and reported in humans. Every year, over 6.5 million people acquire life-threatening fungal infections with 2.5 million attributable deaths. The annual global incidence of invasive aspergillosis was estimated at >2 million with a mortality of 1.8 million. For *Candida* bloodstream infections, annual incidence was about 626,000. In addition, nearly 1 million annual cases of invasive candidiasis with negative blood cultures occurred. About 500,000 annual cases of pneumocystis were documented, with about 80% occurring in persons with HIV infection. The updated global yearly estimate for *Cryptococcal meningitis* was 194,000, with nearly 25% of cases occurring in those without HIV infection or a known immunodeficiency (Denning, 2024).Although fungi act as major pathogens of plants, insects, amphibians, and reptiles, they rarely infect mammals. However, in recent decades, a significant increase in the burden of fungal disease has been observed and reported in humans. Every year, over 6.5 million people acquire life-threatening fungal infections with 2.5 million attributable deaths. The annual global incidence of invasive aspergillosis was estimated at >2 million with a mortality of 1.8 million. For *Candida* bloodstream infections, annual incidence was about 626,000. In addition, nearly 1 million annual cases of invasive candidiasis with negative blood cultures occurred. About 500,000 annual cases of pneumocystis were documented, with about 80% occurring in persons with HIV infection. The updated global yearly estimate for *Cryptococcal meningitis* was 194,000, with nearly 25% of cases occurring in those without HIV infection or a known immunodeficiency (Denning, 2024).

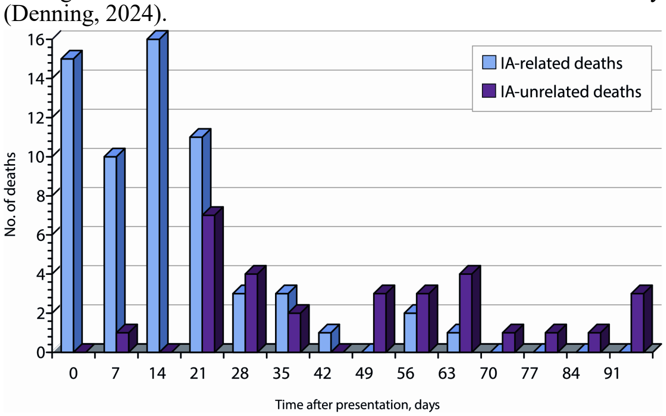

Figure 3: Frequency plot of IA-related and un-related mortality (Garcia-Vidal *et al*., 2015)

Fungal infections are one of the neglected health care infections globally. However, fungal infections cause several deaths and are fatal to human health, but these have long lasting impact. Approximately, 1-2 million people die, and billions of people are affected by fungal infections, still these are underestimated by the health care professionals. Fungal infections are a burden due to their prevalence, impact on vulnerable population and their high risk of antifungal resistance. Another major concern in this aspect is the lack of vaccines. It is estimated that >6 million people suffer from having life-threatening fungal infections annually, with an associated mortality of nearly 3 million. Due to their high frequency, effects on susceptible groups, and growing threat of antifungal resistance, fungal infections constitute a significant worldwide health burden. Clinical manifestations of aspergillosis include invasive aspergillosis, chronic pulmonary aspergillosis, and allergic bronchopulmonary aspergillosis. For invasive aspergillosis, voriconazole is thought to be the first line treatment; in cases of intolerance, resistance, or severe infection. Also, other antifungal medication including echinocandins and amphotericin B formulations can be used. Incorporating various therapeutic approaches offers a more comprehensive clinical picture of the illness and emphasizes the significance of successful anti-fungal treatment in lowering mortality.

Fungal infections result in chronic diseases and if these are left untreated, these can become life threatening. About 400 million people are subjected to the severity of these infections. Serious fungal infections because of weak or suppressed immune system such as AIDS, cancer, organ transplantation and corticosteroid therapies. Early treatment and diagnosis are recommended in this case but neglecting the diseases may lead to chronic illness.

The Need for Vaccines against Fungal Infections:

Fungal infections pose a significant global health threat, with an estimated 1.5 million deaths attributed to these diseases each year (Denning, 2024). The global prevalence of fungal diseases varies widely based on geographical location, socio-economic factors, and underlying health conditions. Candidemia is one of the most common forms of invasive candidiasis and frequently affects hospitalized patients. It is estimated that there are approximately 159,253 cases of candidemia globally each year (PMC5753159). Unfortunately, though there is high burden of fungal infection, and health effects, no FDA approve vaccine is available for animal or human diseases. There are certain challenges associated with fungal vaccines make hurdles in the application of vaccines.

5. IMMUNOLOGICAL BASIS OF FUNGAL VACCINES

Understanding the immunological basis of the fungal vaccine involves exploring host pathogen interactions and mechanisms of fungal immunity, and role of adjuvants in enhance efficacy. Fungal pathogens such as Candida, *Aspergillus*, and *Cryptococcus*, interact with host immune system in complex ways. These interactions begin with recognition of fungal components such as cell wall polysaccharides (β-glucans, mannans, and chitin) by pattern recognition receptors (PRRs) on host immune cells including Toll-like receptors (TLRs), RIG-like receptors and Nod-like receptors (NLRs). Additionally, adaptive immunity is crucial in shielding the host from fungal infections. Specifically, $CD4^+$ T cells play a major role in Th1 and Th17 immune responses. Th1 cells generate cytokines including TNF-α and IFN-γ, which stimulate macrophages and improve their capacity to eliminate fungal infections. Th17 cells, on the other hand, release IL-17, a cytokine that increases neutrophil recruitment and fortifies defenses at mucosal and epithelial surfaces. When combined, these immune reactions enhance fungal clearance and offer more potent defense against infection. For instance, Dectin-1 belongs to the C-type lectin receptor (CLR) family, which controls fungal infections by identifying fungal polysaccharides like β-glucans and initiating immune responses like phagocytosis and cytokine production. Dectin-1 CLR recognizes B-glucans triggering antifungal response. Fungal pathogen can invade immune detection by altering their cell wall composition or producing immunomodulatory factors. *Cryptococcus neoformans* encapsulates itself in a polysaccharide rich capsule impairing phagocytosis. These evasion strategies highlight the need for vaccines that enhance immune recognition and eliminate fungi efficiently (Zaragoza *et al*., 2009).

Importance of Adjuvants:

Adjuvants play a critical role in enhancing the efficacy fungal vaccine by boosting the immune response. These help to overcome the typically weak immunogenicity of fungal antigens by stimulating innate immunity and promoting robust adaptive response. Types of adjuvants include aluminum salts (Alum), oil-in-water emulsions and TLR agonists. For fungal vaccines, adjuvants that target CLRS such as glucans particles have shown promise. Adjuvants enhance presentation by activating dendritic cells and other antigens presenting cells. These also release the pro-inflammatory cytokines and chemokines which enhanced the activation of T-cells and the formation of memory. Recent inoculation focuses on the tailoring adjuvants for specific pathogens. For instance, β-glucans based adjuvants not only serve as antigens but also enhance the immune response through the Dectin-1 signaling (Cassone, 2008).

Target Population for Vaccinations:

Individuals represent high-risk groups that would benefit significantly from effective fungal vaccines (Santos *et al*., 2014). Vaccination could help reduce their susceptibility to IFIs and improve health outcomes.

6. FUNGAL VACCINES AND THEIR DEVELOPMENT (CURRENT APPROACH)

Fungal infections are often underestimated in their impact on human health. Although antifungal medications exist, the rising cases of drug resistance and the limited availability of effective treatments make fungal vaccines a crucial area of research (Oliveira *et al*., 2021). Developing fungal vaccines is challenging because fungi are eukaryotic organisms with complex structures like human cells. Despite these difficulties, various types of fungal vaccines (Figure 3) have been designed and tested, each with unique mechanisms and purposes. Below is a detailed discussion of the kinds of fungal vaccines (Oliveira *et al*., 2021).

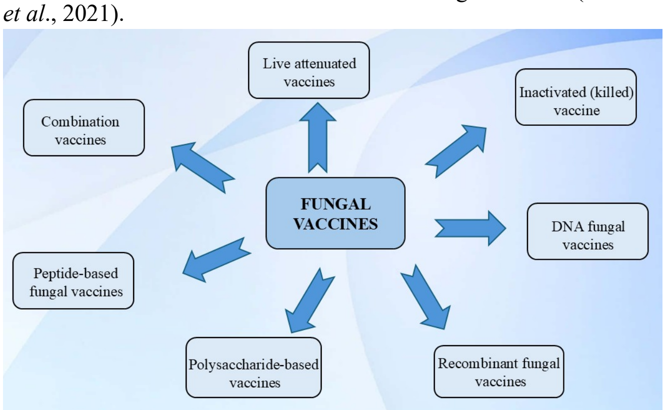

Figure 4: Types of fungal vaccines (Created by Powerpoint)

Live-Attenuated Vaccines (lafvs):

A live-attenuated fungal vaccine is a vaccine based on a viable (live) agent whose pathogenicity has been attenuated (readily multiplies in the body but is unable to produce a serious disease). The resultant immune response, which is very strong and cellular (T-cells) and humoral (antibodies) is like a natural infection but does not produce complete pathogenicity. Live-attenuated vaccines are being explored for *Aspergillus* fumigatus and *Coccidioides posadasii*. The goal of the study was to construct a vaccine candidate against *Aspergillus fumigatus* which is itself a significant contributor to invasive aspergillosis by use of a genetically modified strain lacking the "sglA gene" (8761 octavia; 8761 sglA; 8761-A; (8761 sglA mutant)). The mutation results in the build-up of sterylglucosides (SGs) that are immunomodulatory glycolipids. Accumulation of sterylglucosides changed fungal cell wall and surface antigen, which probably led to an increase in recognition by immune cells. The modifications caused the mutant to be more apparent and more easily recognized by the immune system. For that purpose, both live and heat-killed 20sglA vaccines conferred complete protection against lethal infection (Fernandes *et al*., 2022).

Inactivated (Killed) Vaccines:

Killed fungal vaccines consist of killed fungal cells (e.g. heat-killed), thus these are non-replicative and non-infectious (Liu *et al*., 2011). These retain intact antigenic structures such as cell wall proteins, glycans, glucans, that can stimulate adaptive immune responses without fear of disease. Inactivated (killed) vaccines were being explored for *Cryptococcus neoformans* (Wang *et al*., 2019) by inducing a heat killed *Cryptococcus* mutant strain against invasive mycoses. *Cryptococcus neoformans* is a type of fungus, which typically attacks the lungs with a potential to spread to the brain resulting in meningitis. This happens due to a protein known as "Fbp" that enables fungus to survive and cause a disease. By deleting this protein (producing a mutant named fbp1Delta), this fungus was no longer able to produce severe infections but instead resulted in a "robust protective immune response" in the lungs. For that purpose, mice vaccinated with heat-killed (killed) fbp1D fungal cells that could make them resistant to infection by the virulent form of the fungus in future. The vaccine was effective even when the mice immune system was weakened (without CD4 0 T cells, as it is the case of HIV/AIDS patients) (Wang *et al*., 2019). This study reveals that the "heat-killed fbp1Delta strain may be broad, safe and efficacious vaccine" against various fungal diseases, even in patients with compromised immune system.

DNA Fungal Vaccines:

DNA vaccines are circular plasmid DNA molecule, which have the genetic information of a particular fungal antigen in it (Inácio *et al*., 2023). One promising strategy for avoiding fungal infections is DNA vaccination. These vaccines function by infecting host cells with plasmid DNA that codes for a fungal antigen. After entering the cells, the antigen is generated and presented via MHC class I and class II pathways, which aids inducing humoral and cellular immune responses. This mechanism frequently stimulates Th1 and Th17 immune responses, which are crucial for antifungal defense because these cause the release of cytokines like TNF-α and , IL-17, and IFN-γ. These cytokines improve the body's capacity to eradicate fungal infections by boosting macrophage activity and attracting neutrophils. Heat-shock protein 65, or HSP65, is one antigen that is often researched because it is highly conserved among microbes and can elicit potent T-cell-mediated immune responses, making it an appropriate target for vaccination. Additionally, DNA vaccines have several benefits, including as stability, ease of construction, and the potential to produce long-term immunological memory. However, these still have several drawbacks, such as comparatively low immunogenicity in humans and difficulties with effective DNA transport into host cells, thus more refinement is required before these can be extensively employed in therapeutic settings. This DNA is introduced into the host cells by injection, and a host cell expresses fungal protein to trigger an immune response to both T-cell mediated and antibody-mediated attacks-but there is no live fungus involved. DNA vaccines targeting fungal infections like Paracoccidiomycosis. The gene from *Mycobacterium leprae* called HSP65 is used in a DNA-based treatment (DNAhsp65) in mice infected with *Paracoccidioides brasiliensis*, a fungus that causes PCM. DNA therapy reduced fungal levels in the body, lowered inflammation-related cytokines and improved lung health in the infected mice (Ribeiro *et al*., 2017).

Recombinant Fungal Vaccines:

Recombinant vaccines are the vaccines which stimulate the immune system by making use of certain fungal proteins made in host organisms (such as bacteria or yeast) (Tso *et al*., 2018). These do not carry the same risks as comparable live vaccines and are unaffected by health complications associated with becoming immunocompromised. Recombinant vaccines targeting the rcpa1 for Coccidioides is being tested (Campuzano *et al*., 2024). Coccidioidomycosis is a fungal disease caused by two species: *Coccidioides posadasii* (Cp) and *Coccidioides immitis* (Ci), which are genetically similar but not identical. To prevent that disease recombinant vaccine (rCpa1) was created by using proteins from Cp and tested whether the vaccine could protect against both Cp and Ci (cross-protection). The rCpa1 vaccine worked well in two types of mice: normal (C57BL/6) and humanized mice (carrying the human HLA-DR4 gene) (Campuzano *et al*., 2024). After vaccination, both groups of mice had lower fungal levels in the more immune cells ($CD4^+$ T cells) that produce IFN-γ and IL-17, which are important for fighting fungal infections. The vaccine was effective despite small genetic differences between Cp and Ci. The immune responses mediated by IFN-γ and IL-17, which are linked to T helper 1 (Th1) and T helper 17 (Th17) immunity, play a major role in protecting against fungal infections. Th1 cells and natural killer cells are the primary producers of IFN-γ, which is crucial for activating macrophages. Through enhanced phagocytosis and intracellular death, this activation improves their capacity to engulf and eliminate fungal infections. On the other hand, Th17 cells are the main source of IL-17, which aids in antifungal defense by encouraging neutrophil recruitment to the infection site. These immune reactions work together to create a crucial defense system that aids in the host's removal and management of fungal infections.

Polysaccharide-Based Vaccines:

Polysaccharide vaccines focus on the unique sugar molecules found on fungal cell walls. These vaccines, often conjugated with proteins, enhance immune recognition, some notable features of this type of vaccines are polysaccharides are often poor immunogens on their own, so these are conjugated with proteins to boost the immune response (conjugate vaccines). These vaccines focus on preventing fungi from evading the immune system. *Cryptococcus neoformans* produces a polysaccharide capsule, and vaccines targeting this capsule are being studied. *Cryptococcus neoformans* is a fungus, which may lead to severe diseases, particularly among individuals with ineffective immunity. The fungus uses sugars (EPS) to evade the immune system, which has a polysaccharide capsule. These two are mainly composed of sugar referred to as glucuronoxylomannan (GXM). An experimental vaccine is developed by binding the fungal sugars (EPS) to a protein carrier known as CRM197 to strengthen the vaccine. These also tried two adjuvants (Freund's adjuvant and aluminum hydroxide) to enhance the immune system. The vaccine was administered to mice thrice. When a polysaccharide is conjugated to a carrier protein, such as CRM197, T-helper cells are drawn in, changing the typically T-cell-independent response into a T-cell-dependent one that encourages memory B-cell production, antibody class switching, and long-lasting immunity (Stempinski *et al*., 2025).

Peptide-Based Fungal Vaccines:

Peptide-based vaccines involve short amino acid sequences derived from fungal proteins. These vaccines are highly specific and are being explored for their role in targeting virulence pathways in fungal infections. Some notable features of this type of vaccines are these are highly specific and targeted, reducing the risk of side effects. Easy to produce but may require alum adjuvants to boost efficacy. Vaccines targeting fungal peptides involved in virulence pathways are in the early research phases. However, peptide vaccine against *Cryptococcus neoformans* mp88 is produced.

Combination Vaccines:

Combination vaccines are designed to protect against multiple fungal species or incorporate various antigen types. These vaccines are useful for high-risk populations, such as organ transplant recipients. Some notable features of this type of vaccines are useful for individuals at high risk of multiple fungal infections, such as immunocompromised patients can provide broader protection but requires careful formulation to avoid immune interference (Reyan *et al*., 2022). Combination vaccines targeting Candida, *Aspergillus*, and Cryptococcus are being explored for patients undergoing organ transplants. T-cell immunity role in the development of fungal vaccines protection against fungal infections. These vaccines include multiple antigens that stimulate different parts of the immune system at the same time. As a result, B cells are activated to produce specific antibodies, contributing to humoral immunity. At the same time, T helper cells and cytotoxic T cells are stimulated, which support cell-mediated immune responses. The combined activation of these immune pathways helps create a more balanced and effective defense against infections, vaccines that elicit robust T-cell responses are more likely to be successful, and T-cell-mediated immunity is crucial for protection against fungal infection. Long-term immunity, T-cell-mediated immunity is a crucial factor in the creation of vaccines since it can offer sustained defense against fungal infections. Enhanced vaccine efficacy by determining the best antigen targets and adjuvants, knowledge of the function of T-cell immunity in fungal diseases can enhance vaccine efficacy.

The types of T cells involved are as follows:

1. $CD4^+$ T cells: Also referred to as T helper cells, these cells are essential for coordinating the immune system's defense against fungus infections.

2. $CD8^+$ T cells: Also referred to as cytotoxic T cells, these cells directly eliminate fungal infections.

7. DRAWBACKS AND LIMITATIONS OF FUNGAL VACCINES

The upgradation and progress in the development of vaccines against fungal diseases is prominent, but it did not come alone, here are some drawbacks and challenges of the fungal vaccines.

Immunocompromised Population:

One of the challenges that exist to the development of an effective fungal vaccine is the ability to evoke a protective immune response against the populations who are at high risk of becoming immunosuppressed. The example of this is that individuals with HIV are at high risk of most opportunistic mycoses such as *Cryptococcosis*, *Histoplasmosis* and *Pneumocystis*. According to CDC, HIV/AIDS patients are particularly vulnerable to potentially fatal opportunistic fungal infections such histoplasmosis, cryptococcosis, and *Pneumocystis jirovecii* pneumonia (PJP). An estimated 152,000 cases and 112,000 fatalities worldwide are attributed to *Cryptococcal meningitis* alone, which accounts for a significant fraction of AIDS-related mortality, especially in sub-Saharan Africa where the burden is highest. In addition, $CD4^+$ T-cells required as a protection mechanism against natural infection by these mycoses are significantly depleted in the context of severe lymphopenia that is characteristic of AIDS. The same happens with the immunosuppressed by transplantation or autoimmune diseases (Woodring *et al*., 2022).

Complexity of Fungal Life Cycle and Antigenic Diversity:

Fungal pathogens also have a great level of antigenic variation across and within a species. Because many diseases can alter the proteins expressed on their surface to elude the host immune system, antigenic diversity makes vaccine creation difficult. An immune response developed against one stage of the disease may not be effective against another because various stages of the infection can express distinct surface antigens. The lack of uniform targeting of antigens is made more complex by morphological changes (spores- hyphae yeast). For example, different sets of surface proteins are displayed by sporozoites, merozoites, and gametocytes in *Plasmodium falciparum*, the parasite that causes malaria. The blood-stage merozoites that cause the clinical symptoms of malaria may not be prevented by a vaccination that targets sporozoite surface antigens, but it may prevent the initial infection in the liver.

Limitation of Fungal Vaccine Producing Platforms:

Vaccinations are essential in managing infectious diseases such as viral, fungal, parasitic and bacterial diseases. Genetic recombination vaccines technology is particularly significant in the prevention of human and animal against such pathogens as *Adenovirus*, *Papillomavirus*, *Brucella*, *Listeria*, *Candida*, *Aspergillus*, and *Cryptococcus*. Development of fungal vaccine is challenging as fungal cells are similar to human cells, with complex life cycles making it difficult to target and its immunity is not completely understood. Both healthy and immunocompromised people require effective vaccines. Recently, developed proteomics and systems biology have contributed to the development of new vaccines because of identifying proteins and determining how these act and interact with each other (Hayati *et al*., 2024).

8. OBSTACLES IN DEVELOPMENT OF FUNGAL VACCINES

While the need of the fungal vaccines is evident, their development is still full of challenges that has made it more complex and long-term goal. These challenges include:

Immune Response to Fungi:

Immune response to fungi is one of the biggest challenges in developing the fungal vaccine. Fungi can modify the immune responses in such a way that evade the detection and destruction of the immune system. Some fungi suppress the activation of T-cells such as *Candida albicans* and *Cryptococcus neoformans*. Some fungi pathogens such as *Aspergillus fumigatus* can activate the regulatory immune cells that suppress inflammation which will prevent an effective immune response. So, keeping in view all these mechanisms, such vaccines must be developed that stimulate the robust immune response that not only target the desired fungal pathogen but also combat these immune evasion mechanisms (Casadevall & Pirofski, 2021; Loh & Lam, 2023).

Lack of Research and Funding:

One of the main obstacles in developing the fungal vaccine is the lack of funds for research on the fungal infections. These are overshadowed by bacterial and vaccine, so these are often neglected in global health agendas, which leads to limited funding for research into effective therapies including vaccines. Even though the morbidity and mortality of fungal diseases may compete or even exceed the rates of other bacterial and viral diseases, this low attention is the result of low visibility of the fungal diseases in public health discussion. Antifungal therapies are also very expensive. Many fungal infections remain under-recognized compared to other infectious diseases, so it is difficult to take out the same level of the financial as well as political support for the prevention of such infections via vaccination (Casadevall & Pirofski, 2021).

Diagnostic Barriers:

Fungal infections are not early diagnosed in their course which is another challenging factor in the vaccine development. Many of the fungal infections show symptoms quite similar to the other infections, which lead to the delay in the diagnosis and ultimately in treatment. For example, invasive aspergillosis show flu-like symptoms and diagnosis of it requires the specialized tests which are basically not available in resource-limited settings. Fungi can alter its cell wall thickness in response to the environment. Its immune-stimulating components like chitin and glucans are concealed by the thick cell wall. Also, in some fungi there is a capsule external to the cell wall. It also shields the fungi from the immune system. It further complicates the fungal vaccine development (Cassone, 2008).

Resemblance to the Human cells:

Both human and fungal cells are eukaryotic in nature, so these share many features and many metabolic pathways are quite similar in them. Due to the similarity in function and structure of both cells, vaccine development becomes complicated because the target sites are now narrowed. There are chances of it affecting human cells and causing harm to them. So, it is difficult to target fungal membrane without affecting human cells (Oliveira *et al*., 2021).

9. CONCLUSION

Fungal infections are a major and expanding global health concern, because of their diversity, changing pathogenic patterns, and growing resistance to existing antifungal therapies. To improve diagnosis, treatment, and prevention strategies, a thorough understanding of fungal biology, virulence factors, and host interactions is essential. Advances in antifungal drugs, vaccines, and diagnostic tools offer promising directions. Vaccines could be an effective approach to reduce the impact of fungal diseases but complex fungal biology, immune response against fungal infections, diagnostic barriers and similarity to human host are current challenges in development of fungal vaccines. So, there is a dire need to work on emerging fungal pathogens, resistance patterns, and development of diagnostic tools. Scientists must use different approaches to develop fungal vaccines particularly against diseases having high burden and mortality, keeping in view the challenges associated with fungal vaccines to lessen the burden of medical mycology.

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