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Mucosal membranes, their interactions to microbial infections and immune susceptibility in human hosts

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ABSTRACT: This article presents mucosal immune defense in response to various pathogenic infections in different hosts including man. Internally, the mucosal layer (membrane) covers the respiratory, digestive, nasal, and urogenital systems and serves as a physical barrier against many groups of infections. The host pathogen's interaction with membrane receptors is highlighted in this article, as well as the commensal gut microbiota's protective function in directing both general and targeted immune defense. In order to combat numerous diseases of various types, this review emphasizes the importance of crosstalk between mucosal locations, mucosal adjuvant design, and antigen delivery mechanisms. Additionally, it denotes the function of inflammasomes, lipocalin 2, Muc2 hyaluronan, and probiotics in maintaining homeostasis, regulating the gut microbiota, and enhancing immunological protection against enteric infection and gastrointestinal inflammation. For novel potential vaccines that could activate innate and adaptive immunity in mucosal tissue, there is an urgent need to look for new protective antigens, delivery mechanisms, and mucosal adjuvants. In order to prevent the spread of infections that are drug-resistant, seek protection, and assure host immunological tolerance, this article emphasizes the necessity for new antigens in the construction of new vaccines.

Keywords: Mucosal membrane; Innate and humoral immune defense; Antigen delivery systems; Adjuvants; Vaccines.

1. INTRODUCTION

The mucosal membrane (layer) is found in the gastrointestinal, respiratory, nasal, and urogenital tracts. To pathogens, these epithelial surfaces serve as a barrier. Immune responses are produced by mucus membrane cells against numerous antigens that pass through this lining [1]. However, a variety of microbial infections, nutritional elements, and airborne suspended particles/allergens or antigens are continuously exposed to the gut mucosa [2]. Furthermore, the genitourinary, respiratory, gastrointestinal, and nasal tracts all contain normal commensal microorganisms. These are benign and compete with infectious microorganisms to prevent their binding to receptors on the surface of mucosal membranes. For checking the microbial invasion mucus secreted by gut mucosa obstruct the binding of pathogen at mucosal surface, non-adhered clumping of microbes, creation of acidic environment and secretion of defense peptides infectious successfully remove infection [1]. Symbiotic microorganisms in the gut compete with the pathogen population and monitor mucosal adhesion. Tolerance and deprivation of pathogens must, however, be balanced; otherwise, pathological problems including food

allergies, irritable bowel syndrome, infection susceptibility, and more may develop [2]. The secretion of hydrochloric acid from the stomach's oxyntic cells causes the pH of the surrounding area to become acidic, which also primes the mucosal defence systems of the stomach. The mucus-bicarbonate barrier, which is another barrier, creates a pH gradient on the surface of epithelial cells that is close to neutral pH.

2. MUCOSAL IMMUNE SYSTEM

Internally, the mucosal surface covers a variety of organs and tissues all over the body. Wherever or whenever diseases may enter or spread, it offers defense against them to different hosts. It is a special system in which a number of different compartments produce a strong immune response from both immune cells and defence chemicals to destroy pathogens present inside a specific group of body tissues. Just underneath the mucosal surfaces is this mucosal immune system. The mucosal immune system uses a variety of cellular components, humoral immunity through producing antibodies, and both innate and adaptive immunological protection. The initial line of defence against microbial invasion and food antigens is the mucosal immune system, which can be found in different tracts. Physical barriers (epithelial lining, mucus, cilia activity, intestinal peristalsis, etc.) and chemical elements protect the mucosal lining (pH, antimicrobial peptides, etc.) [3]. Lamina propria tissues and Peyer's patches are also part of the mucosal immune system. Additionally, the IgA mediated immune (IgA) response's activation upholds gut immunological homeostasis. In the gut, epithelial cells directly produce host responses, natural defense, and immunological monitoring. Numerous pattern recognition receptors, such as Toll-like receptor 5 (TLR5), TLR1, TLR2, TLR3, and TLR9, are also expressed by epithelial cells. Additionally, the gastric mucosal epithelium creates chemotactic inflammatory agents and effector cytokines to stimulate both myeloid and lymphoid cells. Lamina propria-associated dendritic cells determine whether an immune response to a certain antigen is inflammatory or anti-inflammatory. The mucosal lining prevents hazardous external substances and germs from entering the body. In addition to serving as a physical barrier, the gut contains specialized cells that release peptides to kill infections as well as gastric juice, which changes the pH of the stomach and upper gastrointestinal tract. Mucosal surface infections are also significant contributors to animal morbidity, mortality, and economic loss [4].

For proper functioning of mucosal immune system structural integrity of the mucosal barrier is highly important [5]. The respiratory, urinary tract and gut mucosal surfaces are regularly exposed with various infectious agents. Due to repetitive invasion of microbes and allergens these become more vulnerable. These are very thin and permeable barriers to the interior of the body for easy transport of gases, nutrients, minerals and water. These membrane barriers maintain important physiological functions such as exchange of gases in the lungs, absorption of nutrients in the gut. These also assist in sensory functions of visual, taste, and olfactory receptors. These membrane barriers also found in throat and uterus and vagina where they also prohibit entry of pathogens. Though, pathogens also choose other routes of entry i.e. receptor binding, but these are major sites of invasion from where pathogens enter into the human body. This epithelial barrier is severely affected by chemicals, mucins, peptides and due to interaction between mast cells and infectious agents. In addition, integrity of mucosal epithelial barriers also depends on the action of immunosuppressive mechanisms implemented on the mucosa [4]. There are numerous immunosuppressants which inhibit binding of pathogens at mucosal surface, inhibition of cell activation, cytokine production, differentiation, and/or proliferation. This mucosal barrier contains tight junctions between the epithelial cells of the mucosa [5]. The mucins found in mucus works as a shield and limit the immunogenicity of intestinal antigens by inducing an anti-inflammatory state in dendritic cells (DC) [6] (Figure 1). Gut mucosal barrier occurs in the stomach checks the back-diffusion of hydrogen ions. This barrier is covered with thick layer of mucus secreted from cells mixed

together with fluid alkaline in nature. This barrier helps to save gastric acid required for digestion. If this mucosal barrier is damaged due to action of acetylsalicylic acid, it leaks acid that diffuses back into the gut mucosa and damages its membrane surface.

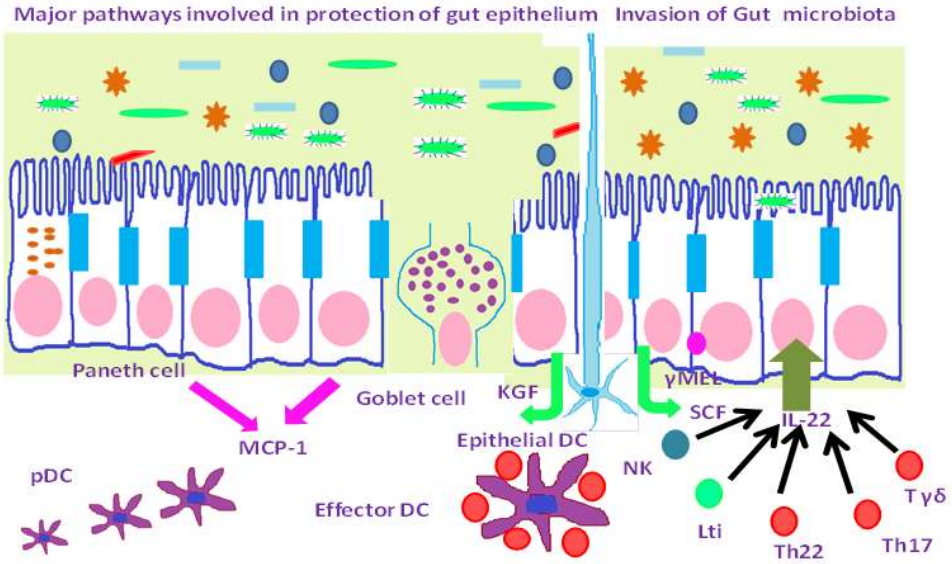

Figure 1. Major pathways involved in protection of gut epithelium.

Mucosa also possess lymphoid tissue that is known as MALT (mucosa-associated lymphoid tissue), it makes first line of defense. Similarly, respiratory tract contains bronchus associated lymphoid tissue (BALT) that protects from inhaled antigens and pathogens. GALT is gut associated lymphoid tissue that possess very loose, barely organized clusters of lymphoid cells in the lamina propria of intestinal villi. It also runs up to Peyers patches, which also found within the intestinal lining. Due to much longer exposure of mucosa surfaces to pathogens, external antigens lymphocytes reside in lower layer in large numbers to operate phagocytosis to kill pathogens at entry point. These immune cells stay inside secondary lymphoid tissue, and found largely distributed throughout the mucosal surfaces [3]. T cells found in outer mucosal epithelial layer contain and participate in immune defense. It is true, approximately 3/4 of all lymphocytes in the body are found in the mucous membranes. Besides this, large numbers of B cells, plasma cells and activated TH cells and macrophages found in loose clusters. The mucosa-associated lymphoid tissue (MALTs) do make body defense by producing large number of antibodies by plasma cells and provides the organism with an important first line of defense (Figures 1 and 2). Spleen and lymph nodes, the tonsils and MALT are secondary lymphoid tissue [7]. MALT also associates dendritic cells, macrophages, innate lymphoid cells, mucosal-associated invariant T cells, intraepithelial T cells, regulatory T cells (Treg), and secreting plasma cells which generate IgA antibodies [1, 3, 8] (Figures 1 and 2).

Gut mucosal surfaces receive large numbers of pathogens through, food and drinking water; these pathogens interact and compete with gut microbiota, and try to invade the mucosa. For invasion pathogens try to bind to some receptors for their entry; but majority of pathogens enter through gut mixed in food or through contaminated water. For protection from pathogen invasion mucosal immune system comes into function to avoid a vigorous immune response to food antigens. Immune surveillance cells and macrophages more efficiently locate, identify and kill microbial pathogens before their entry in the gut. In addition, human gut is heavily colonized by commensal symbiotic microbiota approximately 10^{14} in number. These are highly

beneficial to their host as they compete with pathogenic bacteria and do not provide adhering surface. Thus they replace pathogenic bacteria by occupying the ecological niches in the gut. These commensals generate vitamin K and few components of the vitamin B complex.

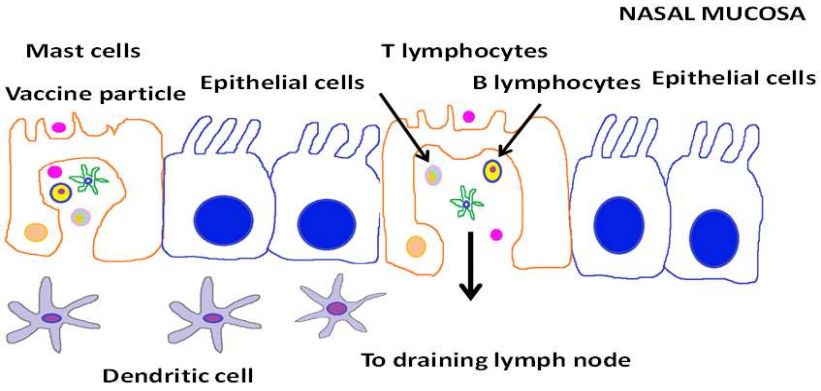

Figure 2. Cellular and vaccine mediated elimination of pathogens by various immune cells.

M cells elimination of infection, by stimulating the innate immune system in mucosa.

3. GUT MUCOSAL IMMUNITY

Mucosal immunity protects the membrane surface from microbial invasion and antigenic assault [9]. Mucosal layers found inside lungs, gastrointestinal tract, respiratory, nasal and urinogenital tract generate immune responses. These try to check invasion of microbial pathogens entering through mucosal surfaces. The epithelial cells of mucous membrane assist in generation of immune response. Few specialized M cells carried the foreign antigen from the lamina of the respiratory, digestive and urogenital tracts to the underlying mucous associated lymphoid tissue (Figure 3). M cells lack microvilli and flat epithelial cells. The antigen is transported across the cell and released into the large basolateral pocket and processed by endocytosis. This antigen activates the B cells in the underlying lymphoid follicles. These activated B cells differentiate into immunoglobulin producing plasma cells, which migrate along the sub-mucosa. Local immune response is generated by neutrophils and various interleukins in the MG.

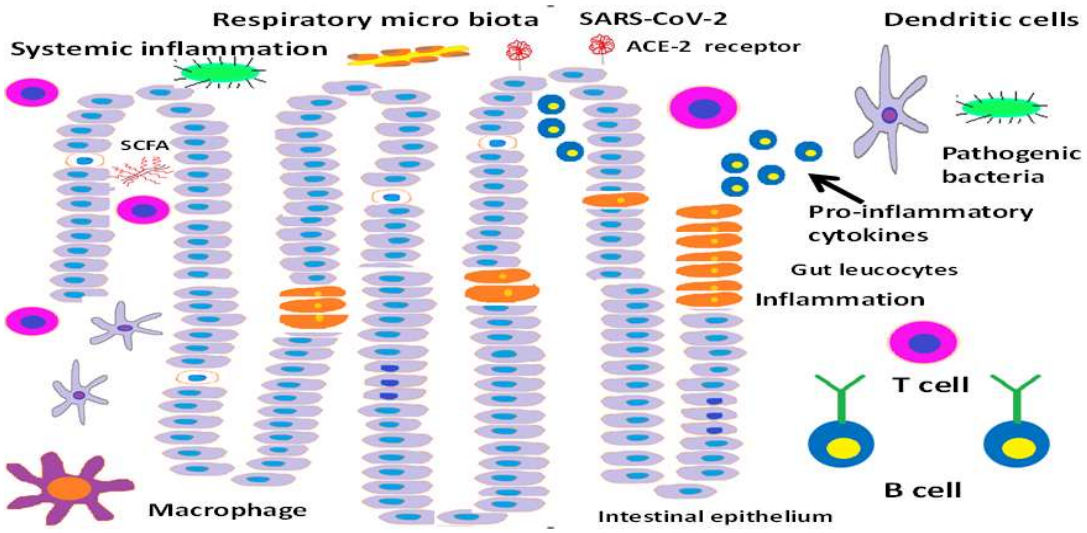

Figure 3. Invasion of respiratory and digestive tract by microbial pathogens elimination of infection immune system in mucosa.

However, gastric mucosa and its associating cells and molecules mainly cytokines actively assists to make innate and adaptive immune responses and protect from gastric diseases [9]. It guards against gastric cancer, noninfectious disorders, and infectious diseases brought on by *Helicobacter pylori*. More specifically, stomach mucosal immunity is crucial for the onset and progression of the illness [9]. Even so, the mucosa of the mammary gland (MG) is a component of the mucosal immune system. It plays an important role in passive mucosal immunity by deploying monocyte macrophages along with intraepithelial lymphocytes in response to infection [10]. Similarly, T lymphocyte-dependent responses are evoked by production and secretion of interleukin-4 in lacrimal glands. Lacrimal gland cells also produce immunoglobulin A (IgA) antibodies. Similar immune response is also generated by major inductive sites of Nasal-associated lymphoid tissue and posterior cervical lymph nodes [11] (Figure 3).

3.1. Immune response to fungal infection

Fungi cause infections in large section of world population and generate life-threatening systemic disease acute to chronic illnesses in them [12]. This spectrum of communicable fungal diseases has been increased enormously in last six decades, besides, common opportunistic primary infection, secondary infections also become major clinical issue with increasing number of cases of immunocompromised patients. These patients display an aberrant type 1 immune response to mucosal fungal infections [13]. Host defense, tolerance and susceptibility is influenced by severity of fungal infections, and patient's immune response. There is a difference in infectivity and pathogenicity among various clinical isolates, because of emerging genetic variations. Similarly, level of antifungal immunity, also differs between mucosa and person's susceptibility to infection. However, there is a need to identify these variables responsible for fungal-host interactions [14] (Table 1).

3.2. Innate immune defense

Fungal infection is a serious global health problem in humans. In response to fungal infection our body prepares organ specific innate and adaptive antifungal immunity [12]. Both types of immune defenses are prepared by immune cells, molecules and receptors. These collectively stand to produce a joint defense against fungal pathogens. In innate immune defense fungal invasion is stopped by non-specific mechanisms mainly by physical barriers, phagocytosis, cytokines, and oxygen dependent and independent mechanisms that is a short term defense. Specific or adaptive immune response is generated by B plasma cells secreted antibodies that are a long-term protection against fungi. In addition, T helper cells (TH1-cell) prepare defense against fungal infection at an earlier stage that is mediated by interleukin-12 (IL-12). Respiratory mucosal layers found inside lungs are heavily infected by major pulmonary fungal pathogens such as *Aspergillus*, *Cryptococcus*, *Pneumocystis*, and endemic fungi [15]. These respiratory fungal infections cause life-threatening invasive diseases and serious clinical problems in humans [15]. This fungal invasion is challenged by innate myeloid cells, including macrophages, dendritic cells (DC), and neutrophils. These cells attempt to strengthen the primary defense through phagocytosis and cytokine secretion. Dendritic cells (DCs) exhibit the ability to recognize fungi-associated information and translate it into qualitatively distinct adaptive T helper (TH) cell immune responses. Natural killer cells do make direct and indirect killing of invading organisms and try to control fungal invasion on body cells [15]. Besides cells various molecules also participate in anti-fungal immune defense. Infected cells secrete cytokine interferon-γ (IFN-γ) molecules which assist with the production of opsonizing antibodies. During antifungal operation, activation of TH1 cells remains instrumental and activates phagocytes at sites of infection (Table 1).

Table 1. Fungal infection of the GI Tract and their immune responses.

Disease	Pathogen	Susceptibility (sign and symptoms)	Transmission	Diagnostic Tests	Immune response	References
Candidiasis	*Candida albicans*	Infection on skin, mouth, throat, gut, and vagina, candidal vaginitis, pain inabdomen	Antibiotics or having a suppressed immune system, multiple factors	Fungal culture	colonization and invasion at mucosal surfaces fluconazole	[19].
Aspergillosis	*Aspergillus fumigattus*	invasive and allergenic disease, inflammation-induced damage, cough; hemoptysis,	Through inhalation of airborne conidia. Contaminate d medical devices	Computerized tomography scan, respiratory secretion (sputum) test, Skin, sputum and blood tests, biopsy	APCs interacting with pathogens, anti-*Aspergillus* immunity	[22]
Cryptococcosis	*Cryptococcus neoformans*	pneumonia-like illness, cough or an aching chest in others, difficulty in breathin	Humans through contact with pigeon droppings or unwashed raw fruit	By isolating Cryptococcus from a sample of affected tissue or direct observation of the fungus by using staining of body fluids	Pattern recognition receptors stimulates the macrophages to release CCL2 to recruit monocytes and dendritic cells (DCs) to the lung	[27]
Phaeohyphomycosis	*Alternaria* sp., *Exophiala jeanselmei,* and *Rhinocladiella mackenziei*. Dematiaceous fungi or melanized" fungi	Skin: subcutaneous nodule or cyst Brain: neurogical symptoms	Breathing in or entry via a cut in the skin of dark filamentous fungi, exposure to soil and vegetation	Microscopic examination of exudates and biopsy specimens, histology, culture, PCR	Pro-inflammatory cytokine production in Card9 KO bone marrow-derived macrophages and dendritic cells	[28]
Hyalohyphomycosis	Moulds, non pigmented fungi *Penicillium marneffei*	Multiple erythematous, subcutaneous nodules; ecthyma gangrenosum-like lesion	Nondematiaceous, hyaline septate hyphal organisms	Isolation of the offending pathogen from clinical specimen (blood, skin, sinuses, lung, others)	$TCD4^+$ lymphocytes or $CD4^+$ T cells make optimal host defense	[28]
Coccidioides immitis	*Coccidioides posadasii* and *Coccidioides immitis*	Fever, cough, chest pain, chills, sputum production, sore throat, and hemoptysis.	Inhalation of airborne spores of *C. immitis* or *C. posadasii*	Chest X-rays or CT scans, detection of Coccidioides antibodies or antigens	Pherules and endospores are recognized by C-type lectin receptors and Toll like receptors	[20]
Histoplasmosis	*Histoplasma capsulatum*	Breathing of spores, fever, cough, and fatigue	Common exposures to bird or bat droppings or soil	Medical and travel history, symptoms, physical examinations, and laboratory tests	Induces a cell-mediated immune response, progression of the cytokine and inflammatory reactions in the lungs	[21]

In response to fungal infection generation of regulatory T cells and the secretion of anti-inflammatory cytokines IL-10 takes place. However, Th1 and Th17 cells prepare anti-fungal defense by secreting various cytokines, interferon-γ, and IL-17 Toll-like receptors (TLRs). Both dendritic cells and immunoglobulins synthesized in response to antigens are best therapeutic candidates which neutralize fungal infections. In addition, epithelial cells and macrophages found in respiratory membrane kill fungal infection by internalization, inflammatory cytokine production, or antimicrobial peptide secretion [15]. Few antifungal peptides (AMP) are also synthesized by body cells to make innate immune defense against fungal infection. These peptides also act as immunomodulatory molecules, which boost the immune response against fungal infections. Similarly, vaccines, checkpoint inhibitors, interferons and colony-stimulating factors also provide primary protection and are used in immune cell therapy [16]. Further, an organ-specific immunity, with tissue-specific tropisms is created to get protection from the major pathogenic fungi [12] (Table 1).

3.3. Role of inflammasomes

Severe inflammation occurs after fungal attack on the skin or mucus surface. Fungal pathogens are identified by PRRs present on the surface of innate immune cells. These cells activate the inflammasome, which is used as the first line of defense against various fungal pathogens. They are large multiprotein complexes anchored by cytoplasmic pattern recognition receptors (PRRs) and are an important part of the innate immune system. Inflammasomes are activated when sensors detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [17]. Moreover, pattern recognition receptors identify these DAMPs which are derived from hosts or attacking microbe. To respond against fungal invasion inflammasomes are formed and activation of the pro-inflammatory protease caspase-1 takes place. This protease caspase-1 cleaves substrates pro-interleukin-1β (IL-1β) and pro-IL-18 into their mature biologically active cytokine forms which make sizable defense against fungal infection in the lung [15]. Though, pathogens have developed effector strategies to antagonize the inflammasome pathway.

More often, dectin-1 expressed on the cell surface are involved in fungal recognition. Furthermore, transduction of signals to the nucleus for transcriptional regulation is made by MyD88 and TRAF6 the adaptor proteins [15]. These proteins act as transcriptional factors which modulate the transcription of a series of genes, especially related to synthesis of chemokines and cytokines. These mediate the generation of cellular and molecular immune responses against a fungal infection and become predominant regulators of infectious microenvironment [15]. In pulmonary mycoses type-2 helper T (Th2) cell responses is generated [18]. T cells play protective roles in making antifungal host defense [13]. The second line of defense is created by inducing adaptive immune system by activating CD4+ T cells, while CD8+ T cells. These type 1 mucosal responses are also generated in other CMC-manifesting diseases (chronic mucocutaneous candidiasis) (Table 1).

4. MUCOSAL INVASIVE MYCOSES

Mycoses is complex fungal-host interaction that generates pathogenesis, and fungal infection initiates at particular site [19]. This is highly invasive and aggressive fungal infection that takes few days to devastate and cause high mortality 50-100% in patients. Fungi of the genera *Aspergillus*, *Candida*, *Histoplasma*, *Blastomyces*, *Coccidioides* and *Cryptococcus* are opportunistic pathogens which cause substantial number of mycoses [20]. Different types of mycoses appear in form of systemic, superficial or subcutaneous diseases. These are caused by fungi, yeasts, molds and *Cryptococcus* and *Histoplasma*. Mucormycosis is caused by *Rhizopus*, *Mucor*, and *Lichtheimia* species. Blastomycosis, is caused by entry of conidia and its growth inside lungs after inhalation. Inside lungs *Blastomyces dermatitidis* mycelial phase converts in to the parasitic

yeast phase. After primary pulmonary infection *B. dermatitidis* elicits a granulomatous reaction that displays fibrotic reaction. It results in a highly fatal clinical pulmonary blastomycosis or chronic pneumonia. In response to mucor immune cells and platelets prepare in antifungal defense. Fungal invasion on immune cells generates virulence, it may be primary or opportunistic; it is opposed by host via immunological defenses [21] (Table 1).

4.1. Aspergillosis

Aspergillus fumigatus is airborne saprophytic fungus, its conidia are inhaled from air and these attach to the respiratory epithelium found in lungs and paranasal sinuses. This fungus grows inside lungs and causes respiratory aspergilloses. Though respiratory epithelium tries to protect, but fungus causes functional defects in circulating neutrophils because heavy doses of systemic corticosteroids enhance cytotoxicity that aids invasive aspergillosis. In response to *A. fumigates* adaptive T-helper (Th) immune responses are generated influence and cause allergic hypersensitivity/detrimental immune patholology. For study of invasive mycoses fungus-specific recognition, signaling, effector pathways and adaptive immune responses to fungal pathogens is highly important [22] .

To achieve early protection against *Aspergillus fumigates*, there is a phagocytosis-dependent activation of the TLR9-BTK calcineurin NFAT signaling pathway that supports innate immunity [23]. Organ transplant patients remain at risk of invasive fungal infection because production of TNF-α in alveolar macrophages gets ceased. This alternatively inhibits TLR9-BTK-calcineurin-NFAT signalling pathway and promotes chances of invasive aspergillosis in organ transplant cases. Patients of SARS-CoV-2 are also threatened by pulmonary aspergillosis (Table 1).

4.2. Candidiasis

Candida albicans is the primary human fungal pathogen causing candidiasis, the most common opportunistic fungal infection of mucosal surfaces. Mucosal infections consisting of oropharyngeal or vulvovaginal candidiasis are caused due to *Candida albicans*. These are life-threatening systemic infections [24]. The disease is believed to be superficial in epidermal and mucosal surfaces, including the oral cavity, pharynx, esophagus, intestine, bladder, and vagina. Deep aspergillosis is seen in alimentary canal, kidneys, liver, spleen, brain, eyes, heart, and other tissues. In deep organs systems aspergillosis is caused due to use of intravascular catheters. Invasive candidiasis is caused due to use of broad spectrum antibiotics, corticosteroids and cytotoxic chemotherapy. Candidiasis fungus secrete candidalysin, peptide, it evokes host immune response to invasive fungi innate mucosal immunity to *C. albicans* [19]. The major defense is prepared by innate mechanisms of epithelial defence against *Candida* fungi. In response to invasion soluble host factors (cytokines, chemokines, antimicrobial peptides, and alarmins) makes effective defence mediated by haematopoietic cells (Table 1).

4.3. Zygomycosis

Zygomycosis is a life-threatening infection in neonates with a distinct pattern of gastrointestinal and cutaneous involvement and high mortality. More than 30 species of Zygomycota are involved in human infections, among them Mucorales is the most abundant. Zygomycosis due to *Rhizopus, Rhizomucor, Absidia, Mucor* species, or other members of the class of Zygomycetes, also causes invasive sinopulmonary infections. An especially life-threatening form of zygomycosis (also known as mucormycosis), is known as the rhinocerebral syndrome, which occurs in diabetics with ketoacidosis. In addition to diabetic ketoacidosis, neutropenia and use of corticosteroids are other major risk factors for zygomycosis. Zygomycetes also invade blood vessels gastrointestinal and skin mainly cutaneous layer [25]. Combination of amphotericin B and surgery

was common management strategy in survivors. Zygomycota and filamentous fungi invade body tissues and show angioinvasion and metastases [26] (Table 1).

4.4. Cryptococcosis

Cryptococcosis is most typically an opportunistic fungal infection that most frequently causes pneumonia and/or meningitis. Cryptococcosis is a caused by basidiomycetes *Cryptococcus neoformans* and *Cryptococcus gattii.* This is an uncommon disease which affects lungs, CNS, skin, bone, eyes and prostate in man. Cryptococcosis is commonly seen in HIV positive individuals. In these patients defective cellular immunity, is a most common risk factor for developing cryptococcosis. Pulmonary cryptococcosis disease occurs in immunocompetent and immunocompromised patients. *C. neoformans* adhere on epithelial cells and lead to fungal internalisation into the respiratory mucosa. Both bronchial and alveolar epithelial responses prepare innate defence against infecting fungus. This disease also appears after organ transplantation, medication with immunosuppressive drugs and chronic kidney diseases [27]. In response to cryptococcal infection antigen-specific Th2 cells and dendritic cell make immune defense inside lungs. In pulmonary mycoses type-2 helper T (Th2) immune responses and priming protective Th17 cell responses are generated against fungal infection [18]. Body also makes adaptive immunity by secretion of protective cytokines (Table 1).

4.5. Phaeohyphomycosis

Phaeohyphomycosis is an infection by brown to black pigmented fungi of the cutaneous, superficial, and deep tissues, especially brain. These infections are uncommon, life-threatening, and occur in various immunocompromised states. Hyalohyphomycosis is an opportunistic fungal infection caused by any of a variety of normally saprophytic fungi with hyaline hyphal elements. For example, *Fusarium* spp. infects neutropenic patients to cause pneumonia, fungemia, and disseminated infection with cutaneous lesions. Chromoblastomycosis (CBM), is one of the most prevalent implantation fungal infections. It is one of the most common of the gamut of mycoses caused by melanized or brown-pigmented fungi [28]. CBM generates initial cutaneous lesion, fibrotic and granulomatous reactions. It also cause series of clinical complications is mainly a tropical or subtropical disease that may affect individuals with certain risk factors around the world [28]. CBM disease generates a nonprotective T helper type 2 (Th2) immune responses with an ineffective humoral type involvement (Table 1).

5. FUNGI-INDUCED AUTOIMMUNE DISEASES

Pathogenic fungi cause a wide range of syndromes in immune-competent and immune-compromised individuals, with life-threatening disease. These are primarily reported in humans with HIV/AIDS and in patients receiving immunosuppressive therapies for cancer, autoimmunity, and end-organ failure [22]. These invasive fungal infections (IFIs) cause high rates of morbidity and mortality in such patients. These patients also come under grip of neutropenia a major risk factor for immunocompromised patients. These patients show aberrant T cell-dependent, type 1 mucosal inflammation and enhanced type 1 immunity rather than defective type 17 responses can promote mucosal fungal infection susceptibility. These responses promote aberrant interferon-γ (IFN-γ)- and signal transducer and activator of transcription 1 (STAT1)-dependent epithelial barrier defects as well as mucosal fungal infection susceptibility [29] (Table 1).

6. IMMUNE RESPONSE TO VIRUS INFECTION

Among the various kinds of pathogenic infections of the host, viral infections constitute one of the most serious public health problems worldwide [30]. Viruses invade mammals mainly humans and parasitize either temporarily or permanent as intracellular obligate parasites. These use host cells for its replication and form complex with host cell DNA. Normally, in humans, viral infections are rarely lethal, because they selectively invade individual cells or tissues. But these are antigenic restructuring in case of SARS, N1H1, Ebola and HIV that give rise pathogenicity and high mortality. These antigenic changes in HIV and influenza viruses are so significant that they devastate host immunity. HIV is one of the most dramatic human examples of an exotic virus killing its host. These viruses obstruct both innate and adaptive immune defense. In most situations, defense against viruses involves multiple immune components, but these could not generate sizable protection against virulence. These viruses have acquired single mechanism that varies i.e. time of invasion and entry into cells, replication and their spread within the host cells (Table 2).

After invasion of human hosts virus interact to cell surface receptors to gets its entry into cells for starting replication. Virus particle in beginning remains unrecognized for the cells of the immune system even host cell is being infected. However, after their replication, class I major histocompatibility complex proteins (MHC class I for short) are able to present intracellular protein fragments to the cell surface. These virus synthesized peptide or fragments of proteins have been identified. In addition, cytotoxic T cell start killing of cells virus infected cells with other with toxic mediators. These cells recognize virus antigens or recognize virally-infected cells with the help of T cell receptors (TCRs) and MHC molecule. Further, cytotoxic factors secreted by T cell population kill the infected cell and, prevent survival of the invading virus (Figure 1). Viruses avoid detection by T cells. Some viruses stop MHC molecules from getting to the cell surface to display viral peptides (Table 2).

Gut mucosa is also attacked by viruses [31] and cause infectious diseases of the gastrointestinal tract [32]. Viruses cause both acute and persistent infections. It includes entry of the virus into the body, multiplication and spread, the development of tissue damage, and the production of an immune response [31]. Primary defense is generated by cytotoxic T cells and NK cells. These cells secrete cytotoxic factors which remain stored inside compartments called granules, in both until contact with an infected cell triggers their release. One of these mediators is perforin, a protein that can make pores in cell membranes. Perforins make pores and assist cytotoxic factors to gain entry into a target cell to facilitate destruction of the cell. Enzymes called granzymes are also stored in, and released from, the granules. Granzymes enter target cells through the holes made by perforin. Once inside the target cell, they initiate a process known as programmed cell death or apoptosis, causing the target cell to die. Another cytotoxic factor is granulysin, which directly attacks the outer membrane of the target cell, destroying it by lysis. Cytotoxic cells also newly synthesize and release other proteins, called cytokines, after making contact with infected cells. Cytokines include interferon-g and tumour necrosis factor-α, and transfer a signal from the T cell to the infected, or other neighboring cells, to enhance the killing mechanisms (Table 2).

Besides this, another immune cell natural killer cells display MHC molecules on its surface it releases toxic substances, in a similar way to cytotoxic T cells; it kills the virally-infected cell. These cells recognize cells which possess reduced number of MHC class I molecules on their surface When the NK cell finds a cell displaying fewer than normal MHC molecules it releases toxic substances, in a similar way to cytotoxic T cells, which kill the virally-infected cell.

Table 2. Important virus infections of the gastrointestinal tract and their immune responses.

Disease	Pathogen	Susceptibility (sign and symptoms)	Transmission	Diagnostic Tests	Immune response	References
COVID-19	SARS-CoV-2	Fever, dry cough, muscle pain, loss of taste, red eyes, headache, diarrhea	Exposure to respiratory fluids carrying infectious virus	ELISA, RT–PCR, genome sequencing, serological tests	Cytokine storm, viruses dampen anti-viral IFN responses by evading the innate immune cells, destruction of lung cells	[34, 35]
Diarrhea	Rotavirus	Very contagious virus	Fecal-oral route, severe watery diarrhea, fever and vomiting.	Physical examination Oral or intravenous fluid replacement	Innate immune response leads to the induction of type I and type III interferons (IFNs) and other cytokines	[44]
Enteric diarrhea	Enteric adenovirus	Diarrhea accompanied by vomiting, low grade fever and mild dehydration	Transmitted via the fecal-oral route	Antigen detection, polymerase chain reaction (PCR), virus isolation, and serology	Adaptive *immune response* comprises virus-specific antibodies	[44]
Diarrheal illness	Astrovirus	Common symptoms of gastroenteritis, nausea, stomach ache, loss of appetite, body aches	Fecal–oral route; contaminated food and water	Medical history, and various blood and stool tests, EIA Enzyme-linked immunosorbent assay, Polymerase chain reaction (PCR) tests	Host body generates antibody-mediated immune response. Fluid replacement for dehydration	[44]
Influenza	Influenza type A virus	Fever, chills, muscle aches, cough, congestion, runny nose, headaches and fatigue	People with flu can spread it to others up to about 6 feet away. Most experts think that	Viral culture, serology, rapid antigen testing, (RT-PCR), immunofluorescence assays, and rapid molecular assays	Influenza-specific humoral immune response by production of secretory IgA antibodies locally, its transepithelial transport along the mucus layer of the respiratory tract	[69]
Upper respiratory infections and oral disease in cats	Calicivirus	Nausea, vomiting, diarrhea, abdominal pain, and a low fever	Fecal–oral and vomit–oral routes. Sporadic and outbreak cases are spread mainly by person-to-person contact; contaminated food or water	Viral isolation, identification by a PCR (polymerase chain reaction) test or immune-histochemical staining	Both humoral and cellular elements that help to control and eradicate the infection	[69]
Viral pneumonia	Respiratory syncytial virus	Infections of the respiratory tract decrease in appetite, Wheezing	Through contact with droplets from the nose and throat of infected people	Chest X-ray or CT scan, mouth swab or blood test	Production of virus-neutralizing antibodies and T-cell-specific immunity	[69]
Polio	Poliovirus	Person's brain and spinal cord	Through infected fecal matter entering the mouth, food or water containing human feces and less commonly from infected saliva	Oligonucleotide mapping (fingerprinting) or genomic sequencing	Humoral' or serum immunity, opv produces antibodies	[112]

Interferons synthesized and released by virus infected cells make strong defense against viruses. These effectively inhibit replication in viruses, by directly interfering with their ability to replicate within an infected cell. They also act as signaling molecules that allow infected cells to warn nearby cells of a viral presence. Interferons signal neighboring cells to increase the numbers of MHC class I molecules upon their surfaces, so that T cells surveying the area can identify and eliminate the viral infection.

After virus invasion on gastrointestinal tract, antiviral secretory IgA antibodies found at mucosal surface play a major role in clearing viral infections and preventing or modifying disease after re-exposure [33]. Virus is neutralized by antibodies before they get the chance to infect a cell. Antibodies specifically recognize invading pathogens and bind (stick) to them in large numbers. Antibodies bind virus particles to stick together in a process called agglutination. Agglutinated viruses make an easier target for immune cells than single viral particles. A third mechanism used by antibodies to eradicate viruses, is the activation of phagocytes. A virus-bound antibody binds to receptors, called Fc receptors, on the surface of phagocytic cells and triggers a mechanism known as phagocytosis, by which the cell engulfs and destroys the virus. Finally, antibodies can also activate the complement system, which opsonines and promotes phagocytosis of viruses. Complement can also damage the envelope (phospholipid bilayer) that is present on some types of virus.

The human body is home to a diverse microbial community of commensal microbiota [30]. However, the integrity of the commensal microbiota is disrupted by invading viruses [30]. These microbes colonize speedily to fight against viral infection and disease in humans [34]. These alter host susceptibility and thereby suppress infectivity to certain viral diseases and influence vaccine immunogenicity. The gut microbiota also influences the progression of respiratory viral infections via metabolites and helps generate immune responses against pathogens. Gut microbiota also play important role in termination of severe SARS-CoV-2 infection [34]. These also check secondary bacterial infections caused by immune disorders and inappropriate use of antibiotics. Coronavirus grows in upper respiratory tract and adhered with mucosal membrane cause sneezing and coughing and severely inflammation of trachea, bronchus and gastric mucosal tissue. Virus spike protein binds with ACE-2 receptors found on human gastric intestinal cells. Virus multiplies very rapidly and entered inside gut epithelium and infiltrate in to liver and kidney and other tissues. Virus causes serious respiratory bursts and sepsis and generates cytokine storm and immune response in patient sepsis, dry cough, fluid filling and cytokine burst in lungs. Cough, congestion, thick spot of bronchus [35]. Angiotensin-converting enzyme 2 is expressed in both the lungs and the small intestine, which may be a bridge between the lung and the gut. These mechanisms involved in the interaction between SARS-CoV-2 infections and the gut microbiota can be used treatment or prevention of severe SARS-CoV-2 infections by improving gut microbial homeostasis [34]. Microbiota showed therapeutic effects against COVID-19 infection [36]. Gut microbiota also contribute anti-virals used in HCV treatment [37] (Table 2).

Gastrointestinal infections cause mucosal damage, primarily crypt enterocyte necrosis (crypt abscess) in the small intestine and colon. These also cause lymphoid necrosis and destruct Peyer's patches. Virus attack cause serious, even life-threatening disease via the mucosal route. Furthermore, viral mucosal infections can give way to secondary events, such as infections with other potentially more dangerous pathogens, or alterations of the immune system, such as development of allergies. Passive transfer of virus-specific antibodies has been used in experimental and clinical settings to prevent or treat viral mucosal infections. In the future, the development of new mucosal vaccines promises to have the strongest impact on the epidemiology of viral infections [38].

African green monkeys avoid SIV disease progression by preventing intestinal dysfunction and maintaining mucosal barrier integrity [39]. AGMs from developing intestinal dysfunction and the subsequent chronic inflammation that drives both HIV disease progression and HIV-associated comorbidities [39]. Moreover, intestinal mucosa of acutely SIV-infected macaques, secrete interleukin-7 (IL-7) that triggers chemokine expression and immune cell homing into mucosa and generate mucosal immune responses. IL-7 is a potent mucosal adjuvant to stimulate the FGT female genital tract of macaques immune system and elicit vaginal antibody responses to local immunization. It ably confers protection against many sexually transmitted diseases [40]. This rs-IL-7gly prepares the mucosa to respond through the chemokine-dependent recruitment of immune cells, and do the activation of mDCs and the formation of TLSs. The localization of DT-specific IgA+ plasma cells in the upper vaginal mucosa produces specific immunoglobulins in the vaginal secretions. Regulatory T cells (Treg) play a critical role for immune homeostasis, but may inhibit pathogen-specific immunity in infectious disorders [41]. Regulatory T cells (Treg) possess unique properties like effector functions are highly useful in neurotropic virus infections (Table 2) [41].

Copathogenesis of respiratory viral and fungal coinfections is complex and involves a dynamic interplay between the host immune defenses [42]. Recently in COVID-19 patients mucormycosis is caused by black fungus, it has attacked large numbers of patients. Reason behind its growth is long term use of antibiotics. It is rare but dangerous infection that is caused by getting into contact with fungus spores in the environment. It can also form in the skin after the fungus enters through a cut, scrape, burn, or another type of skin trauma. Invasive pulmonary aspergillosis (IPA) is the most common fungal pulmonary infection in severely immunocompromised patients. *Aspergillus* species are commonly isolated from the soil, plant debris, and the indoor environment, including the hospital with invasive pulmonary aspergillosis [42]. Severe black fungus was also grow in patients infected with coronavirus disease 2019 (COVID-19) pandemic [42]. It complicates the SARS-2 caused pneumonia and cause disease severity and mortality (Table 2).

7. IMMUNE RESPONSES TO PROTOZOAN INFECTION

Protozoans are cellular parasites which cause many infectious diseases in humans. These are major health burden in the developing world and contribute significant morbidity and mortality in human and animal population[43]. Protozoan diseases are often chronic these persists for months or years. There are many protozoan parasites *Plasmodium, Entamoeba histolytica Trypanosoma, Leishmania, Toxoplasma gondii, Giardia intestinalis* or *Giardia duodenalis, Cryptosporidium parvum*, *Cyclospora cayetanensis, Pneumocystis* which cause severe pathogenesis in organisms [44]. Some of the most prevalent and deadly human diseases, including sleeping sickness, amoebic dysentery, and malaria, are caused by single-celled parasites. These parasites vary in their structural and biochemical properties and quite distinct patterns of specific and innate immune responses. Both *Plasmodium* and *T. gondii* do anatomic sequestration, and change their surface antigens such as *Trypanosoma, E. histolytica* alter host immune response by nonspecific and generalized immunosuppression. Few highly lethal attacks are made by human African trypanosomiasis, chagas disease and lesihmaniases [45]. Few protozoans such as *Trypanosoma, Leishmania* and *T. gondii* develop resistance to immune effector mechanisms (Table 3).

Immune responses against protozoan parasites are generated by different hosts by employing cells, molecules with well adapted mechanisms and pathways. Innate immunity protects at earlier stage of infection by employing cells and molecules, but it also assists in preparation of a long term specific immune response by generation of antibodies for neutralization of pathogens [46]. Though large numbers of pathogens are phagocytozed by macrophages, but many of them replicate within macrophages and develop resistance to

phagocytic killing. Non specific factors found in serum component also kill protozoan parasites. Besides this, antibody-dependent cytotoxic reactions also kill *T. cruzi* and *T. brucei gambiense* parasites. In addition, repetitive infection in animals generates trypanolytic factor that provides resistance against *Trypanosoma brucei brucei*. In response to protozoan body synthesize selected immunoglobulins and cytokines which act as immunotherapeutic agents. Antibodies are quite specific which neutralize selected antigen and play a major role in immune defense against parasites. *T. brucei gambiense* antigens are recognized by T helper cells and engulfed by macrophages, processed and presented to B cells to produce antibodies that evoke potential humoral immune response. Cellular defense mechanism is made by emplying CD4+ T-lymphocytes and activated macrophages against protozoans. These act as effector cells and are regulated by release of cytokines. In response to *Plasmodium* attack body makes diversity of defense mechanisms either cellular or humoral, it depends on secretion of antigen from protozoa's parasite (Table 3).

In response to parasite invasion host body generate strong host immune responses that result in a high incidence of immunopathology. Inflammasome is a multimeric protein complex. It makes host immunity against protozoan parasites [47]. Nod-like receptors and the inflammasomes regulate innate immunity against bacterial pathogens [48]. Toll-like receptor (TLR)/MyD88 signaling pathway regulate immune response to opportunistic pathogen *Toxoplasma gondii* [49]. Protozoan parasites evade the immune responses of the host, and also survive in an immunocompetent animal. Natural killer (NK) cells are first line effector cells which control protozoan infection at an initial stage. Natural killer cells secrete IL-12 dependent IFNγ that efficiently kill protozoan infected cells and parasites by generating cytotoxic response. These cells also play effector functions as they also secrete IL-10 and IL-17. NK cells evoke innate immune responses during different protozoan infections [46]. Robust immunity is recruited against disease pathogens by making concerted action of many innate and adaptive cell populations including macrophages, neutrophils, dendritic cells, CD4+, and CD8+ T cells and B cells among others [50] (Table 3).

In a condition, when body is attacked by a diverse and complex group of protozoa (Apicomplexan), *Toxoplasma gondii, Plasmodium, Cryptosporidium, Eimeria* and *Babesia* species. It is challenged by natural cells and try to make primary defense [46]. These infections are often associated with considerable variability in clinical presentation [43]. Cellular immunity is evoked in host body that is an important defense mechanism in leishmaniasis and toxoplasmosis. Various cytokines are released from Th (T helper cells) and Tc -cells (cytotoxic T cells) which control both the immune response and pathology in host body. However, Th1 helper cells secrete gamma interferon (IFN-α), and interleukin-2 (IL-2) and induce cell-mediated response. While Th-2 helper cells produces IL-4 and IL-6, which induce antibody-mediated immune response. Secretion of various cytokines stimulates cell division and clonal expansion of T and B-cells. This leads to a rapid increase in antibody production and/or cytotoxic T-cell numbers. Infected cells are killed by pyroptosis that is activated by human and mouse caspase-1, human caspase-4 and caspase-5, or mouse caspase-11 [51]. In pyroptosis in inflammatory caspases attack infection and make clear of pathogens [51]. In *Trypanosoma cruzi* infection interleukin-17 mediate innate immune functions [50]. Thus a balanced immune response is made by effector and cellular mechanisms. These sporozoite-specific antibodies are highly useful for successful immunization (Table 3).

Table 3. Protozoan Infections of the gastrointestinal tract and their immune responses.

Disease	Pathogen	Susceptibility (sign and symptoms)	Transmission	Diagnostic Tests	Immune response	References
Cryptosporidiosis	*Cryptosporidium parvum*, *C. hominis*	Watery diarrhea, nausea, vomiting, cramps, fever, dehydration, and weight loss, watery diarrhea, loss of appetite, increased gas and nausea	Contact with feces of infected mice, birds, farm animals; ingestion of contaminated food or water; exposure to contaminated water while swimming or bathing	Stool O&P exam, enzyme immunoassay, PCR	Recruitment of innate immune cells such as NK cells, dendritic cells, macrophages and mast cells	[44, 47]
Toxoplasmosis	*Toxplasma gondii*, Apicomplexan	Multisystem organ failure, Systemic infection. ingestion, Hepatitis blindness and mental retardation, pneumonitis	Ingestion of raw or inadequately cooked infected meat	immunoglobulin G (IgG) tests	Production of pro-inflammatory cytokines and chemokines	[44]
Microspordiosis	Microsporidia	Diarrhea and wasting	Encephalitozoon intestinalis in ground water	Biopsy or in stool, urine, CSF, sputum, or corneal scrapings	Innate immune system can partially eliminate the infection by various immune cells	[44]
Pneumocystosis	*Pneumocystis carinii* or *Pneumocystis jiroveci*	Dry cough, problem in breathing, night sweats	PCP spreads from person to person through the air	Bronchoalveolar lavage, lung tissue biopsy	Active role of $CD4^+$ and $CD8^+$ T cells	[44]
Amoebiasis (amoebic dysentery)	*Entamoeba histolytica*	From mild diarrhea to severe dysentery and colitis; abscess on the liver, Abdominal pain fatigue, weight loss, diarrhea, blotting and fever	Fecal-oral route; ingestion of cysts from fecal contaminated water, food, or hands, Sewage, non treated drinking water, flies in water supply	Stool O&P exam, enzyme immunoassay Both innate and adaptive immune	CTL is activated by APC and cytokines from innate immune cells and Th cell and then innate immune	[45]
Cyclosporiasis	*Cyclospora cayetanensis*	Explosive diarrhea, fever, nausea, vomiting, cramps, loss of appetite, fatigue, bloating	Ingestion of contaminated food or water	Stool O&P exam using ultraviolet fluorescence microscopy	T cell subsets in peripheral mononuclear cell and membrane interleukin-2 receptor (mIL-2R)	[47]
Balantidiasis	*Balantidium coli*	Ingestion, diarrhea, abdominal pain, and sometimes a perforated colon	Intestinal symptoms, infected by eating and drinking contaminated food and water that has come into contact with infective animal or human fecal matter	Endoscopy. cysts colonoscopy or sigmoidoscopy to obtain a biopsy from the large intestines	Hyperemy, oedema, haemorrhagia and ulcers	[47]

Disease	Pathogen	Susceptibility (sign and symptoms)	Transmission	Diagnostic Tests	Immune response	References
Chagas disease or American trypanosomiasis	*Trpanosoma brucei*	Acute fever, irreversible damage to heart, esophagus and colon	Chagas disease, is spread mostly by insects in the subfamily Triatominae, known as "kissing bugs". The symptoms change over the course of the infection	Microscopic examination of blood smears. ELISA or ICT test *T. cruzi* (ELISA, HAI, or IIF)	Dysphagia and regurgitation, and megacolon, leading to severe constipation and faecal retention	[50]
Leishmaniasis	*L. donaovani, L. major, L. mexicana, L. brazileinsis*	Skin ulcers, mucocutaneous complications, and visceral disease	The bite of infected female phlebotomine sand flies. The sand flies inject the infective stage (i.e., promastigotes) from their proboscis during blood meals	Light-microscopic examination of stained slides, molecular methods, parasitological, or serological tests	T cells play a major role in generating specific and memory T-cell responses to intracellular parasitic infections	[51]
Giardiasis	*Giardia lamblia*	Diarrhea, nausea, stomach cramps, gas, greasy stool, dehydration if severe; sometimes malabsorption syndrome, diarrhea, abdominal discomfort, blotting, flatulence	Oral-fecal, hand to mouth. contaminated fomites; ingestion of contaminated food or water, pipe leaks, ground water pollution, sharing of water source by humans and wildlife	Stool O&P exam; ELISA, direct fluorescence antibody assays	Strong immune responses characterized primarily by the production of anti-parasite IgA	[58]

Hematuria, anemia, impaired growth, renal, hepatic and spleen failure.

Table 4. Bacterial infections of the gastrointestinal tract and their immune responses.

Disease	Pathogen	Susceptibility (sign and symptoms)	Transmission	Diagnostic Tests	Immune response	References
Tuberculosis	*Mycobacterium tuberculosis*	Phlegm, cough with blood, fever, shortness of breath, or swollen lymph nodes	Through the air, not by surface contact. Person to person	TB skin test (TST) and TB blood tests	Conventional CD4 and CD8 T cells, but also γδ T cells and CD1 restricted T cells. γδ T cells recognize phospholigands	[57]
Shigellosis or bacterial diarrhea	*Shigella*	Shigella infection has diarrhea (sometimes bloody), fever, and stomach cramps.	Via the fecal–oral route, including through direct person-to-person or sexual contact or indirectly through contaminated food, water, or fomites	Bacterial culture and genetic tests, Neutrophils in fecal smear	Humoral *response* mediated by mucosal sIgAs and systemic IgGs directed against the LPS O-antigen	[62]
Acute diarrhoeal infection	*Vibrio cholerae*	Nausea, severe diarrhoea, vomiting, or watery diarrhea, dehydration and lethargy	Spread by eating or drinking food or water contaminated by the feces (poop) of an infected person	Selective media culture, stool dipsticks or darkfield microscopy	Cellular immunity appears to be one that leads to $CD4^+$ T cell differentiation to both Th1 and Th2	[76]

Disease	Pathogen	Susceptibility (sign and symptoms)	Transmission	Diagnostic Tests	Immune response	References
Sores, ulcers, stomach cancer	*Helicobacter pylori*	Dull or burning pain	From contaminated food, water, or utensils	Blood, stool, and breath tests, endoscopy	Strong systemic immune response, infiltration of neutrophils, B- and T-cells into the gastroduodenal mucosa	[80]
Scarlet fever	*Streptococcus pyogenes*	Nausea or vomiting, sore throat, enlarged neck lymph nodes, swollen tonsils, tender tonsillar exudate, bad breath, or headache	Through droplets when someone with the infection coughs or sneezes, or through shared food or drinks	Positive Lancefield group A antigen test	Primary defense by innate immune cells	[81]
Mild flu-like illness, pneumonia-type illness	*Legionella*	Cough, fever, chills, shortness of breath, muscle aches, headaches and diarrhoea	Breathe in small droplets of water in the air that contain the bacteria	Urinary antigen test (UAT)	macrophage to release cytokines which attract the attention of natural killer cells.	[80] [82]
Typhoid fever.	*Salmonella typhi*	High fever, headache, stomach pain, weakness, vomiting and loose stools. Treatment includes antibiotics and fluids	Infect the intestinal tract and the blood	Analyzing samples of blood, poo, or pee examined under a microscope	recruitment of phagocytes and IFN-γ production	[83]
Cholecystitis, bacteremia	*Pasteurella multocida*	Bloating, vomiting, nausea, fever, yellow skin	Gallbladder inflammation, tenderness of the upper right portion of the abdomen, altered mental status, or decreased food intake	Ultrasound	Th1-mediated proinflammatory immune response	[85]
Plague	*Yersinia pestis*	Fever, chills, headache, fatigue and muscle ache	Get plague after being bitten by a rodent flea that is carrying the plague bacterium or by handling an animal infected with plague	Specific and rapid F1 Ag DFA, ELISA, and the dipstick test, PCR	Primary defense is prepared by lymphocytes, Subunit vaccines comprised of the *Y. pestis* F1 and LcrV proteins	[86]
Proliferative enteropathy	*Lawsonia intracellularis*	Anorexia, wasting, diarrhoea, reduced appetite	Proliferative enteropathy	From infected livestock	Th1-type cellular immune response	[92]
Urinary tract infection (UTI)	*Esherichia coli*	Pelvic pains, increased urge to urinate, pain with urination and blood in the urine	Bacteria live in or vagina, genital areas, urethra, travel to the bladder, and cause an infection	Analyzing urine sample	Recruitment of inflammatory cells	[92]

Most of the gut related protozoan infections are transmitted through contaminated food and water. *Cryptosporidium parvum* or *C. hominis and G. lamblia* cause severe gastrointestinal infections in human population. Another protozoan *Entamoeba histolytica* cause amoebic dysentery. *G. lamblia* attach to the intestinal mucosa by using a large adhesive disk made up of microtubules. These chronic infections cause intermittent diarrhea, phlegm, pain, bloating, and weight loss. These pathogens use exosomes to deliver virulence and effector molecules to host cells. They are nanoskeletal, membrane-bound vesicles, extracellular components that facilitate cell-to-cell communication and maintain homeostasis in normal and pathophysiological conditions. They manipulate the immune response and regulate infection [44] (Table 3).

Digestive system remains exposed with numerous bacteria, fungi, viruses and parasites which also compete to each other and gut commensals. These infectious agents invade mucous membrane and damage it. In response to mucous membrane starts preparing innate and adaptive immune responses and maintain homeostasis, during infection and inflammation. Microbiota or flora which colonizes inside host gut compete and interact with parasites. These parasite-microbiota interactions control infection and disease [52]. *Giardia spp*. is a gut microbiota *Giardia duodenalis* it is controlled by proliferation of gut microbiota [53]. Colonization and growth of gut microbiota-modulate host immune responses against parasites [54]. These also inhibit parasite colonization and its establishment by secreting inhibitory secondary metabolites. Mucin2 is a protein that lowers down host-microbe interactions, and check microbe adhesion [55]. Nonenteric protozoal diseases such as microsporidia, trypanosomatids, *Toxoplasma* spp., *Neospora* spp., are mostly seen in immunocompromised people, mainly HIV infected patients [56] (Table 3).

8. BACTERIAL INVASION OF MUCOSAL MEMBRANES

There are thousands of bacterial parasites which cause pathogenesis and diseases in man. Many of these diseases are of zoonotic origin. Bacteria invade host body by forming attachment to cells. These grow very rapidly, proliferate and release toxins which severely damage host cells. In response to bacterial infection host body generates both innate and adaptive immune responses. But development of resistance against intracellular growth of bacteria is very tedious. Most of the bacterium show intracellular growth, and also cause delayed type hyper sensitivity and induce cell mediated immune response. In case of intracellular growth of bacteria innate immune defense remains ineffective. But cytokines secreted by CD4 cells play important role including IFN y, which activate macrophages to kill ingested pathogens more effectively. Bacteria possess few specific structures through which they attach to the host surface. Gram negative bacteria possess long hair like projections or pilli which are used to associate and stick at the surface of digestive tract. Few other bacteria secrete adhesion molecules which attach to both the bacteria and the ciliated epithelial cells of the upper respiratory tract. Secretary IgA molecules block bacterial attachment to mucosal epithelial cells and prepare main host defense against bacterial attachment. In human society most common infections seen are tuberculosis, salmonellosis, chlamydiosis, campylobacteriosis, Lyme disease, toxoplasmosis, giardiasis, cryptosporidiosis [57]. COPD pathogens such as *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* have a significant impact on the aging population [58] (Table 4).

Staphylococcus aureus, Salmonella enterica, Escherichia coli, Streptococcus pneumoniae and mycobacteria are highly invasive bacterial infections these cause inflammation, activate autoreactive lymphocytes and generate lupus symptoms [59]. Among them respiratory and gastrointestinal tract infections are more serious. Influenza and other respiratory viral infections are the most common forms of acute respiratory infections [60]. Bacterial dysbiosis induces various changes in host cell machinery. Bacterial infections trigger overgrowth, dissemination chronic inflammation and cause sepsis) [61] (Table 4).

9. IMMUNE RESPONSE TO BACTERIAL INFECTION

9.1. Role of lymphocytes

T lymphocytes, natural killer cells and macrophages prepare innate immune defense. These also control interaction of host-bacteria [62] and first line defense against bacterial infections [63]. Innate lymphoid cells (ILCs) are a group of functionally heterogeneous but potent innate immune effector cells. These work as tissue-resident sentinels against intracellular and extracellular bacterial infections. role of the different ILC populations in various bacterial infections and the possible ways of immune evasion [63] (Figure 2). In response to bacterial infection ILCs secrete cytokines which are used in pathogen killing. Mast cells (MCs) become active very quickly against acute bacterial infections, phagocytose bacterial cells, and finish it [64]. However, during chronic infections MC engulf large numbers of in infectious cells and stop pathological sequellae [64].

NK cells quickly interact with epithelial cells, fibroblasts, macrophages, dendritic cells, and T lymphocytes. These assist in preparation of immune homeostasis and generation of immune responses. NK cells which secrete IFN-α, stimulate additional NK cells from peripheral blood that amplifies the anti-bacterial immune response. Thus, NK cells participate both in physiological and pathogenic processes to maintain gut immunity [65]. In response to bacterial infections inflammasome activation takes place. These are multi-protein signaling platforms that trigger the maturation of the pro-inflammatory cytokines, interleukin-1β (IL-1β) and IL-18, and cause large cell death. Inflammasomes act as sensors and detect microbial and host-derived molecules [66]. ILCs found near to mucosal barrier play important role in homeostasis and respond rapidly to the pathogens and employ immune cells [62] (Figure 2). IL-17 producing cells activate both innate and adaptive immunity against infectious diseases at the mucosa [67] (Table 4, Figure 4).

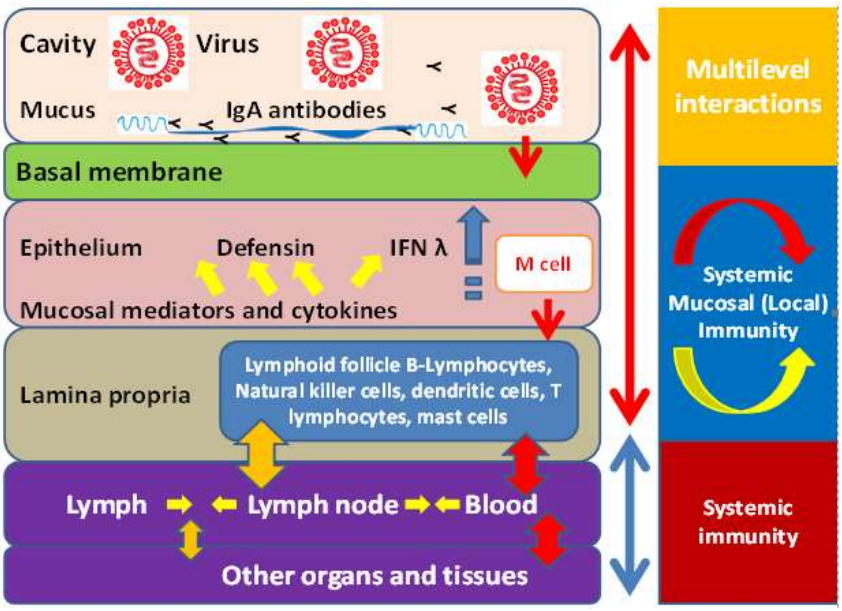

Figure 4. Multilevel interactions of immune cells, molecules to virus pathogen in gut mucosa and generation of systemic mucosal immunity.

9.2. Gut microbiota and pathogen interaction

Gut of vertebrates including humans and other mammalian species are colonized by large, diverse, and dynamic community of commensal bacteria, or microbiota. These commensal bacteria stay on the mucosal surfaces of the gastrointestinal tract and the respiratory tract. Trillions of bacteria mainly microbiota is colonized

inside gut and play important role in immune responses and inflammatory disease [68]. These native commensal microbes provide many metabolic advantages to their hosts, promoting immune homeostasis, immune responses and protection from pathogen colonization. These form a physical barrier against microbial invaders and toxins. These major involvements of the intestinal barrier include luminal microbes, mucin layer, gastrointestinal motility and secretion, enterocytes, immune cells, intestinal vascular barrier, and hepatic barrier. Commensal bacteria also inhibit pathogen growth and their colonization. They form a physical barrier against microbial intruders and toxins. This is mediated by multiple mechanisms, including direct killing, competition for limited nutrients, and enhanced immune responses [68] (Figure 4).

Gut microbiota promotes and maintains host immune homeostasis during bacterial infections [69]. These gut microbiota secret certain metabolites which play protective roles in bacterial pneumonia [69]. Gut micro flora maintains bacterial translocation that is performed by pathogen-associated molecular patterns, such as lipopolysaccharide, from the gut lumen to the mesenteric lymph nodes, systemic circulation and other normally sterile extra-intestinal sites [70]. This is also essential for formation of anti-microbial antibodies [71]. Symbiotic bacterial translocation tries to check overgrowth of potentially pathogenic bacteria in cirrhotic patients [72]. Gut commensal microbes imprint intestinal immune cells with the innate receptor SLAMF4, which activates lymphocytes and acts as an immunomodulator of intestinal immunity (Figure 4). It contributes gut immune protection against enteric pathogens [73]. Gut non symbiotic microbes enhance the proliferation of potentially pathogenic bacteria species [60]. These impose pervasive effects on gut physiology, metabolism, immunity and health of host [52]. Microbiota manages bacterial translocation, cause inflammation and infection during liver cirrhosis [72].

Intestinal infections are often caused by pathological translocation of gut bacteria or endotoxins resulting from intestinal barrier dysfunction [74]. Killing of gut microbial population give rise gastrointestinal disorders and cause secondary bacterial infection [75]. Gut microbiota maintains bidirectional interactions with infectious agents, either through direct microbiota-microorganism interactions or indirectly through various stimuli of the host immune system. These play highly protective role against significant infections during early childhood [76]. The gut microbiome provide resistance against colonization of pathogenic bacteria enteric infection [77]. These provide protection to exogenous microorganisms mainly against bacterial enteric infection [78] and raise subsequent immune responses [79] (Figure 4).

Gut microbiota colonize very rapidly, competing for nutrients and supporting intestinal barrier integrity [78]. In patients with severe burns, major surgery, hemorrhagic shock, or severe acute pancreatitis, intestinal infections lead to more serious common complications such as sepsis and multiple organ dysfunction syndromes. *H. pylori* infection cause peptic ulcers, chronic gastritis and gastric adenocarcinomas and mucosa-associated lymphoid tissue lymphomas [80]. Virulent strains of *Streptococcus pyogenes* drives systemic infection and lowers down immunity [81]. *Klebsiella pneumoniae* causes serious infection and pneumonia-derived sepsis and extracellular lymphatic metastasis in human. It results in high morbidity and mortality [80] [82]. *Klebsiella pneumoniae* antibiotic-resistant strains become hyper virulent cause very severe pneumonia, urinary tract infections, bacteremias, and liver abscesses. It is treatable by interleukin-17 (IL-17). *Salmonella Typhimurium* heavily invade murine gut absorptive epithelium [83] and causes severe gastrointestinal infection, inflammation and enteric infections [84]. All these effects remain asymptomatic. Alcohol-induced intestinal microbiota may be associated with intestinal barrier dysfunction because the micro-biota and its products modulate barrier function by affecting epithelial proinflammatory responses and mucosal repair functions [85].

For control of microbial infectious diseases both mucosal and systemic immunity play important role [86]. Primarily host immunity is maintained by physical barriers and specialized immune cells, whose failure mechanisms leads to severe pathogenesis. More specifically, innate immune responses are generated by epithelial and endothelial compartments check bacterial infection at site of invasion [87]. Microbial pathogenesis in gut cells is also controlled by certain antibiotics such as norfloxacin. This antibiotic induces immunomodulatory effects, including pro-inflammatory inducible nitric oxide synthase, down regulation of cyclooxygenase-2 and NF-κB, upregulation of heme oxygenase-1 and IL-10 expression, an important prophylactic play a role [88]. These antimicrobials rapidly eliminate pathogens, allowing a quicker return to health and longer survival. The presence of the micronutrient selenium in selenoproteins can modulate pathogen virulence, microbiome diversity, and host immune responses during bacterial infections [89].

10. MUCOSAL PROTECTION AND THERAPEUTICS

Various therapeutic methods and strategies have been developed to finish mucosal lining infection in respiratory, digestive and urinary tract. Though, natural protection is made by antigen-presenting cells (APCs) [90] and mucosa-associated invariant T cells [91]. APCs process external signals and evoke both local and systemic responses and generate immune tolerance. Mucosa-associated invariant T cells raise intestinal immunity by secreting antibacterial immune defense molecules which prevent gastric diseases [9] (Figure 4). Innate or non specific defense is against bacterial pathogens is made by C-type lectin receptors [89]. LCN2 (lipocalin) and Muc2 protects from colitis by disassociating pathogenic in colonic mucosa. It also limits tissue damage and translocation of pathogenic and commensal bacteria across the epithelium [92]. Lipocalin 2 (LCN2) binds to bacterial siderophores and obtsruct iron supply to them [93].

Hyaluronan is a glycosaminogly can polymer that protects experimental mice from *Citrobacter rodentium* infection and intestinal inflammation. It also maintains homeostasis and modulates the gut microbiota and immunity in enteric infection and inflammation in gastrointestinal tract. Hyaluronan is used in gut microbiome-targeted immunotherapy [94]. Cytokine signaling assists in epithelial regeneration and triggering immune responses in the digestive tract [95]. After bacterial infection transcription of the upd3 cytokine in Drosophila enterocytes is regulated by Hippo, TGF-β, and Src-MAPK pathways [95].

Probiotics are mixtures of live bacteria and yeasts; these are also commercially available in processed and fermented dairy products such as yoghurt. These boosts up host's gut health and immunity and compete with infections microbes. These compete with pathogenic bacteria and check their colonization by secretion of inhibitory metabolites. Daily consumption of *Lactobacillus casei* strain, (LC+mcra) consumption over-produce probiotics that inhibits harmful bacteria, boost the immune system and increase resistance to infection. These effectively prevent growth of food borne enteric pathogenic infection of *Salmonella* and diarrheagenic *E. coli* [96]. Biofilm is a group of microbiome having different bacterial colonies or single type of cells found in a group. These found adhered and embedded in an extracellular matrix. These can colonize in various human cells and tissues. These undermine the host safe responses by forestalling resistant location and polarizing the safe responses towards a mitigating state, advancing the diligence of bio-film-implanted microbes in the host [97]. At long last, there is a cooperative connection between blood bunch articulation and development of the gastrointestinal microbiome [98]. Mammalian microRNAs and long non-coding RNAs assume significant part in the host-bacterial microbe connection [99]. These miRNAs tweak fiery reactions, cell infiltration, and oversee inborn and manage nonspecific and specific immune responses [100]. These induce immunity and inflammatory responses in bacterial infection (Figure 4). These miRNAs bacterial minicells, microswimmers, and OMVs can

go about as attainable medication transporters [61]. These make prompt immune response and evoke provocative inflammatory reactions in bacterial infection [101] (Figure 4).

11. MUCOSAL VACCINES

In response to pathogenic attack immune cells like lymphocytes, memory cells and APCs (antigen-presenting cells) found in mucosal layer make larger non-specific or innate immune defense. In general mucosal defense is prepared by antibodies, secretary molecules and immune cells [102]. Furthermore, these mucosal sites could work as attractive targets for vaccine design [103]. After finding and selection of particular antigen, B lymphocytes start converting in to B plasma cells or antibody secreting cells. Its clonal expansion at mucosal sites, involving secretory antibody responses and tissue-resident T cells, it leads to induction of specific defense or adaptive immunity. Evoking of specific immunity prevents initiation and establishment of an infection and development of disease symptoms [103]. In response to antigen delivered resident lymphocytes mainly plasma cells generate antibodies and secretion in the gut kill harmful bacteria. Protection of mucosal surfaces is done by using mucosal vaccines based on protective antigens molecules. These generate sizable immunity and responds equally against infectious agents and their secreted antigens [102]. Naturally, specific defense is also generated at these mucosal sites, by resident T cells, B plasma cells and APCs that successfully prevents an infection to occur. But due to development of drug resistance in pathogens there is an immense need for improved mucosal vaccine formulations. For development of mucosal vaccines, selection of novel antigen, adjuvant for its safe delivery be needed. Antigen mixed in oil emulsion of adjuvant prevents physical elimination and enzymatic digestion of antigens and track the route of its transport and presentation. Both systems easily target mucosal inductive sites including membrane, or M, cells. These might capable of elimination of infection, by stimulating the innate immune system to generate effective adaptive immunity. These provide protection against enteric and respiratory pathogens of neonates [102] (Figure 3).

For protection of parasitic infections so many mucosal vaccines have been generated. Among them, adjuvant subunit antigens, RNA and DNA based injectable vaccines have been prepared but are unlicensed. Contrary to this, all live attenuated and inactivated whole-cell vaccines are successful and get licensed [103]. An alum-based vaccine was prepared by using SARS-CoV-2 spike protein subunit 1 as an antigen. This protein antigen generates strong antiviral defense after synthesis and secretion of antibodies against mucosal SARS-CoV-2 virus in mice. It promotes anti-SARS-CoV-2 systemic and mucosal immunity in experimental animals [103, 104]. These respiratory virus vaccines generate large numbers of antibodies which ably neutralize the virus infection, these also induce both cellular and humoral immunity and clear primary infection and also protect against secondary infection through memory cell population. However, live attenuated vaccines protect against viral pathogens by generating mucosal antibody responses in respiratory tract [105].

11.1. Mucosal delivery systems

Various delivery systems have been developed for transfer of antigens and mucosal adjuvants. These delivery systems work at the interface between passive and active immunity. For this purpose, live attenuated bacterial vectors are also used to deliver adjuvants through mucosal surfaces. For delivery of protective antigens live attenuated vaccines bacterial or viral vector systems are also used. In addition, live bacterial vectors which carry attenuated strains of *Salmonella typhi* or *S. paratyphi*, Bacille Calmette-Guérin or *Bordetella pertussis*. These also carry commensal bacteria, such as lactobacilli or certain *Streptococci and Staphylococci.* Both live bacterial and viral vectors have been made which could successfully deliver antigens. DNA vaccines are also prepared by encoding protective antigens. These more efficiently induce immune responses and provide wider

protection against microbial pathogens which colonize or invade mucosal surfaces [106]. Besides this, various lipid-based structures liposomes, immunostimulating complexes (ISCOMs) have been developed. These easily entrap antigens and deliver them at the site of infection. Besides this, different types of biodegradable particles have been made either by using starch or copolymers of lactic and glycolic acid. Few mucosa-binding proteins mainly plant lectins and bacterial proteins were also used for this purpose. These either modulate or stimulate production of various cytokines. VLPs virus-like particles or pseudoviruses are also used for antigen delivery. These are self-assembling, non-replicating viral core structures, prepared from non-enveloped viruses. It's recombinant structures are used to produce secretory IgA molecules and generation of CTL mucosal immune responses against mucosal gut pathogens.

11.2. Mucosal adjuvants

For making more efficacious vaccines identification of safe and effective mucosal adjuvants are highly required. For generating neutralization potential of antibodies new innovative antigens and delivery methods are to be searched. Few potent mucosal adjuvants for cholera toxin have been made. New mutants of cholera toxins (heat-labile enterotoxins) have been prepared by removal of ADP-ribosylation property responsible for its toxicity. Similarly, hybrid protein toxins were prepared by fusion of protein A (CTA1-DD) from *Staphylococcus aureus* with cholera toxin A1 subunit. This toxin is selectively intake by B cells and work as an antigen. It is very safer but needs proper and efficient adjuvant for delivery to the operation site. In another method CTA1-DD is loaded into ISCOM particles function as an mucosal adjuvant, it strengthen both humoral cellular immune responses. ISCOM works as an adjuvant and a carrier for delivery of antigens through oral route [107]. Besides this, synthetic oligodeoxynucleotides with unmethylated 'CpG motifs' (CpG ODN) which also represent and express Toll-like receptor were used to construct artificial bacterial DNA [108]. Plant viral vectors are also used to deliver intranasal delivery of antigens for effective stimulation of mucosal immune responses in animal [109].

The protective HIV-1 envelope gp41 antigen P1 acts as a mucosal adjuvant stimulating the innate immunity. It induces production of cytokine and chemokines, intracellular signaling pathways, mucosal dendritic cell (DC) activation, and T cell proliferation. P1 also acts as adjuvant for other mucosal vaccines; it stimulates both humoral and cellular antigen-specific responses [110]. But it is very difficult to prepare adjuvants to deliver vaccines at site of infection caused by HIV-1 and HSV-2. It could become possible by using sub-unit vaccine antigens (i.e., HIV-1 gp140 and HSV-2 gD) that can be delivered with Poly(I:C) or CpG1668. It works like an adjuvant and induces long-lasting virus-specific immunoglobulin (Ig)-G and IgA antibodies in the vagina and feces. SOSIP-gp140 booster is provided to induce mucosal immunity and anti-viral protection in sub-unit vaccines. It acts as a mucosal IL-4R antagonist HIV and induces high-quality cytotoxic CD4+/CD8+ T cells and humoral responses in macaques. It boosts up mucosal immunity and effectiveness of HIV-1 vaccine by generating large numbers of functional antibodies in the blood, which ably combat mucosal infection caused by HIV-1 [111]. By using novel antigens of virus origin, its genetic material or genes can be used to have mucosal vaccines. These might successfully neutralize SARS-CoV-2 antigens. Inactivated poliovirus vaccine (IPV) is also prepared, its administration potentially blocks poliovirus transmission and induce mucosal immunity [112]. It blocks viral replication in individuals via induction of a robust mucosal immune response in the intestine and secret enteric neutralizing IgA [113]. Similarly, administration of AIVs mucosal vaccines successfully prevents Avian Influenza A Virus infection. This is safe and efficacious mucosal vaccine that mimics the natural infection route and cut off the AIVs infection route [114] (Table 5).

Table 5. Important antivirus vaccines available in the market with its dosage and immune efficacy.

Pathogen	Trade name	Composition	Dosage	Immunological mechanism	Efficacy	References
Rotavirus	Rotarix, Rota Teg	Live attenuated, monovalnet or pentavalent rotaviruses	Oral 3 doses	Mucosal IgA and systemic neutralizing IgG, over 70- 0% against severe disease	High	[102]
Poliovirus	Orimune, OPV Polymyelitis vaccine	Live attenuated trivalent, bivalent and moconvalent polioviruses	Oral 3 doses	Mucosal IgA and systemic IgG, over 90% in most of the world	High	[103]
Salmonella typhi	Vivotif, Ty21A	Live attenuated Salmonella typhi bacteria	Oral 2-3 doses	Mucosal IgA, systemic IgG and CTL, responses variable, but more than 50%	High	[104]
Vibrio cholera	Dukora, ORC-Vax, Shanchol	Inactivated V cholera O1 classical and E1 Tor biotypes with or without CTB	Oral 2-3 doses, toxin-specific, LPS-specific IgA	Strong herd protection over 85%	High	[105]
Influenza type A and B virus	Flumist	Live viral re-assortment with trivalent mix of H1, H3 and B strains of hemagglutinin and neurominindase genes in an attenuated donor strain	Intranasal in young children, 2 doses	Hemagglutinin and neurominindase-specific mucosal IgA and systemic IgG responses >85% in children variable in adults	Moderate	[102]

12. CONCLUSION

The epithelial cells of mucous membrane play an important role in promoting the immune response by delivering the foreign antigens from the lamina of the respiratory, digestive and urogenital tracts to the underlying mucous associated lymphoid tissue. Thus, mucus layer found in digestive tract assists in maintaining homeostasis and plays important role in regulation of host-microbe interactions. These exogenous antigens are carried by specialized M cells across the cell and released into the large basolateral pocket. Where plasma cells generate antibodies. More often, delivery of various antigens with the help of mucosal adjuvants and delivery systems work at the interface between passive and active immunity. In response to pathogenic attack immune cells, mainly macrophages, dendtritic cells, T cells, B cells and all memory resident cells make long term larger defense against pthogens. In general mucosal defense is prepared by antibodies, secretory molecules and immune cells. Innate lymphoid cells (ILCs) mainly lymphocyte prepare innate immune defense. Further, infectious agent is attacked by inflammasomes, large multi-protein complexes scaffolded by cytosolic pattern recognition receptors (PRRs). In addition, hyaluronan is a glycosaminoglycan polymer that plays important role in homeostasis and modulating the gut microbiota and immunity in enteric infection and inflammation in gastrointestinal tract. Muc2 protects against lethal infectious colitis lipocalin 2 (LCN2) an innate immunity protein. Probiotics are good antimicrobials which work against certain microbes as well as improving host's gut health and immunity.

Further, gut microbiota play important role in pathogen colonization, immune responses and inflammatory disease. These indigenous symbiotic microorganisms provide many metabolic benefits to the host and promote immune homeostasis, immune responses and protection against pathogen colonization Various mucosal antigen delivery systems and mucosal adjuvants have been developed. These could work as attractive

targets for mucosal vaccines. These vaccines are safe and highly efficacious; mimics the natural infection route and cut off infection. These vaccines boost up mucosal immunity by generating large numbers of functional antibodies in the blood. Live attenuated bacterial vectors are used to deliver through mucosal surfaces. These DNA vaccines, encoding protective antigens induce immune responses and/or protective immunity to pathogens that colonize on or invade through mucosal surfaces. There is a need to search new protective antigens which could act as a mucosal adjuvant stimulating the innate immunity. The main subject is to explore possibilities to design new vaccines to control invasion of drug resistant pathogens; new adjuvants can provide more immune tolerance to host.

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