Russian Journal of Infection and Immunity = Infektsiya i immunitet
2025, vol. 15, no. 3, pp. 465–475

Инфекция и иммунитет
2025, Т. 15, № 3, с. 465–475

INTERACTIONS BETWEEN VIRAL AND BACTERIAL PATHOGENS IN INFECTION DEVELOPMENT: A REVIEW WITH AN EMPHASIS ON HERPES SIMPLEX VIRUS (HSV)

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Abstract. The interaction between viruses and bacteria has a significant impact on human health, affecting various microbial ecosystems in the respiratory and urogenital tracts as well as in cases of ventilator-associated pneumonia. These interactions can be complex and contribute to the development of diseases. Some interactions benefit the virus directly, while others indirectly create conditions favorable for bacterial growth. For instance, viruses can damage epithelial cells, disrupt the immune system, and alter the composition of the microbiota, making the host more susceptible to bacterial infections. Conversely, bacterial species can influence viral infections by altering the host environment and potentially contributing to viral transmission. Herpes simplex virus (HSV) is a common infection caused by two types, HSV-1 and HSV-2, which can lead to various illnesses ranging from mild mucocutaneous infections to severe neurological and systemic complications. HSV-1 is often associated with cold sores, while HSV-2 primarily causes genital herpes. Both viruses are highly contagious and spread through close contact. While there's no cure, antiviral medications can manage symptoms and reduce transmission. The prevalence of HSV-2 varies globally and is influenced by factors such as geographic location, gender, and sexual behavior. The virus can cause a wide range of symptoms depending on the infection site and the individual's immune system. HSV can interact with various bacterial species to influence the development and progression of disease. For example, it can exacerbate periodontal disease by creating conditions favorable for bacterial growth or increase the risk of acquiring bacterial infections such as *Staphylococcus aureus* and *Acinetobacter baumannii*. Conversely, some bacteria, like *Lactobacillus crispatus*, can inhibit HSV infection. Additionally, HSV can interact with bacteria in specific disease contexts, such as increasing the severity of ventilator-associated pneumonia or facilitating bacterial urinary tract infections. Moreover, bacterial vaginosis is associated with an increased risk of HSV-2 acquisition. Overall, this review underscores the necessity for ongoing research into viral-bacterial interactions, particularly focusing on HSV, to enhance our understanding of disease pathogenesis and improve therapeutic and public health strategies.

Key words: *bacterial infection, co-infection, herpes simplex virus, host microbial interactions, public health, viral infections.*

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Для цитирования:
Калантар Нейестанаки М.Х., Мехдипур А. Взаимодействия между вирусными и бактериальными патогенами в развитии инфекций: обзор с акцентом на вирус простого герпеса // Инфекция и иммунитет. 2025. Т. 15, № 3. С. 465–475. doi: 10.15789/2220-7619-TIB-17749

Citation:
Kalantar Neyestanaki M.H., Mehdipour A. Interactions Between Viral and Bacterial Pathogens in Infection Development: A Review with an Emphasis on Herpes Simplex Virus (HSV) // Russian Journal of Infection and Immunity = Infektsiya i immunitet, 2025, vol. 15, no. 3, pp. 465–475. doi: 10.15789/2220-7619-TIB-17749

DOI: http://dx.doi.org/10.15789/2220-7619-TIB-17749

ВЗАИМОДЕЙСТВИЯ МЕЖДУ ВИРУСНЫМИ И БАКТЕРИАЛЬНЫМИ ПАТОГЕНАМИ В РАЗВИТИИ ИНФЕКЦИЙ: ОБЗОР С АКЦЕНТОМ НА ВИРУС ПРОСТОГО ГЕРПЕСА

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Резюме. Взаимодействие между вирусами и бактериями оказывает значительное влияние на здоровье человека, затрагивая различные микробные экосистемы в дыхательных и мочеполовых путях, а также в случаях вентилятор-ассоциированной пневмонии. Такие взаимодействия могут быть сложными и способствовать развитию заболеваний. Ряд взаимодействий могут непосредственно поддерживать жизненный цикл вируса, в то время как другие косвенно создают условия, благоприятные для роста бактерий. Например, вирусы могут повреждать эпителиальные клетки, нарушать иммунную систему и изменять состав микробиоты, делая организм хозяина более восприимчивым к бактериальным инфекциям. И наоборот, бактерии могут влиять на вирусные инфекции, изменяя гомеостаз организма хозяина и потенциально способствовать распространению вируса. Вирус простого герпеса (ВПГ) первого и второго типа (ВПГ-1 и ВПГ-2) вызывает распространенную инфекцию, проявляющуюся как в виде легких слизисто-кожных инфекций, так и в виде тяжелых неврологических и системных поражений. ВПГ-1 часто ассоциируется с герпесом на губах, в то время как ВПГ-2 в первую очередь вызывает генитальный герпес. Оба вируса крайне контагиозны и распространяются при близком контакте. Хотя существующие лекарства не приводят к элиминации вирусов, противовирусные препараты способны контролировать симптомы и снижать их распространение. Уровень инфицирования ВПГ-2 варьирует в разных странах и зависит от таких факторов, как географическое положение, пол и сексуальное поведение человека. Вирус может вызывать широкий спектр симптомов в зависимости от места инфицирования и сохранности иммунной системы человека. ВПГ может взаимодействовать с различными видами бактерий, влияя на развитие и прогрессирование заболевания. Например, он может усугублять пародонтоз, создавая условия, благоприятные для роста бактерий, или повышать риск заражения бактериальными инфекциями, такими как *Staphylococcus aureus* и *Acinetobacter baumannii*. И наоборот, некоторые бактерии, такие как *Lactobacillus crispatus*, могут препятствовать заражению ВПГ. Кроме того, ВПГ может взаимодействовать с бактериями и утяжелять течение пневмонии, связанной с искусственной вентиляцией легких, или способствовать формированию бактериальных инфекций мочевыводящих путей. Более того, бактериальный вагиноз связан с повышенным риском заражения ВПГ-2. В целом представленный обзор подчеркивает необходимость постоянного исследования вирусно-бактериальных взаимодействий, особенно роли ВПГ, для улучшения понимания патогенеза заболевания и улучшения терапевтических стратегий и тактики здравоохранения.

Ключевые слова: *бактериальная инфекция, коинфекция, вирус простого герпеса, взаимодействия микробы–хозяин, общественное здравоохранение, вирусные инфекции.*

Introduction

The interactions between viruses and bacteria have recently emerged as a focal point of study due to numerous significant examples involving human pathogens of clinical relevance. However, despite their likely importance in applied and health sciences, the ubiquitous interactions between viruses and bacteria have yet to be thoroughly reviewed or compiled. While it has long been recognized that bacteria and eukaryotic viruses coexist, attention to their relationships, particularly in terms of promoting or inhibiting each other's presence in their eukaryotic hosts, has only relatively recently gained traction. Although co-infections among different pathogens, including those spanning multiple kingdoms, have been well-documented, many questions remain regarding the mechanisms and extent to which these pathogens, along with their interactions with other microbes, contribute to varying infection levels. Infectious diseases are primarily caused by viruses or bacteria that frequently interact with one another. Although their presence may precede subsequent infections, viruses, and bacteria can exist in the body without causing any special symptoms. They often inhabit the same niches, yet only recently has there been growing interest in their potential collaboration in promoting wellness or disease states. While the interaction of certain bacteria and viruses, such as the influenza virus, is well understood, researchers typically prioritize identifying the location of the infection over the manner of cooperation. There are two main types of interactions between bacteria and viruses that cause disease: direct interactions that benefit the viruses in some way, and indirect interactions that benefit bacteria. Direct interactions that promote viruses occur when the virus utilizes a bacterial component to facilitate entry into the host cell. Conversely, indirect interactions lead to heightened bacterial pathogenesis due to viral infection. Enteric viruses primarily utilize the direct pathway, whereas respiratory viruses predominantly impact bacteria indirectly [1].

Understanding the interactions between viral and bacterial infections is crucial for effective management and prognosis determination in patients. These interactions can significantly impact the course

of disease and treatment outcomes. For instance, herpes simplex virus (HSV) infection is one of the most common sexually transmitted infections in humans and can have serious implications for both individual health and public health. Therefore, elucidating the relationship between HSV and various bacterial infections is vital. Research has shown that viral infections can predispose individuals to secondary bacterial infections or exacerbate existing bacterial infections. This phenomenon is often observed in respiratory infections, where viral pathogens like influenza viruses weaken the immune response, making individuals more susceptible to bacterial superinfections such as pneumonia. Conversely, bacterial infections can also influence viral infections [3].

Understanding the mechanisms underlying these interactions is essential for developing targeted therapeutic strategies. Furthermore, understanding how viral and bacterial pathogens interact in the host can inform the development of new therapies, such as combination therapies that target both pathogens simultaneously, providing insights into the dynamics of disease transmission and informing public health actions. By understanding how viral and bacterial pathogens interact in hosts and spread among populations, public health officials can implement more effective control measures to prevent outbreaks and reduce disease burden [30]. This review highlights key knowledge on the complex interplay between viral and bacterial infections, with a particular focus on herpes simplex virus (HSV).

Herpes simplex virus

Herpes simplex virus encompasses types 1 and 2 (HSV-1 and HSV-2), which manifest in a wide array of illnesses, ranging from mucocutaneous infections to infections of the central nervous system (CNS) and sporadic infections of visceral organs, some of which can pose life-threatening risks. The term “herpes” derived from the Greek word meaning “to creep” has been documented in medical literature since ancient times. Cold sores, also known as herpes febrile, were noted by the Roman physician Herodotus around AD 100. Genital herpes was first detailed by John Astruc, a physician to the king of France, in 1736, with the initial English translation of his treatise on venereal disease emerging in 1754. Transmission of infection through orolabial lesions was observed in the late 19th century. Experimental transmission of the disease to rabbits was achieved in the early 20th century, and the ability to culture HSV *in vitro* was established in 1925. In the 1960s, Nahmias and Dowdle identified two antigenic types of HSV, each with distinct sites of viral recovery [7, 33, 47].

The eight human herpesviruses (HHVs) are categorized into three groups based on their genomic and biological characteristics: alphaherpesviruses (such as HSV-1, HSV-2, and varicella-zoster virus [VZV]), betaherpesviruses (including cytomegalovirus [CMV], HHV-6, and HHV-7), and gammaherpesviruses (such as Epstein–Barr virus and Kaposi sarcoma-associated herpesvirus, or HHV-8). Herpesviruses share certain morphological traits, such as an internal core containing double-stranded DNA, an icosahedral capsid comprising 162 capsomers, an amorphous tegument surrounding the capsid, a lipid envelope containing surface viral glycoproteins, and an average diameter of approximately 160 nm. However, despite these structural similarities, each herpesvirus exhibits distinct biological and epidemiological features. Although HSV-1 and HSV-2 are closely related to herpesviruses, they exhibit distinct serological and genetic characteristics. The genome of HSV consists of a linear, double-stranded DNA molecule with a molecular weight of approximately 1×10^8 kDa, encoding around 90 transcriptional units, of which 84 are believed to encode proteins. The genome features repeated sequences at both terminal ends, organized in an inverted fashion, thus dividing it into two unique components. While HSV-1 and HSV-2 share approximately 50% overall sequence homology, homologous sequences are distributed throughout the entire genome. Most polypeptides encoded by one viral type are antigenically related to those of the other viral type. However, there are also type-specific regions unique to HSV-1 and HSV-2 proteins, some of which play a role in evading host immunity. Despite diverging 6 to 8 million years ago, interspecies recombinants of HSV-1 and HSV-2 are widely circulated. HSV demonstrates genomic stability, and methods such as restriction endonuclease or sequence analysis of viral DNA can distinguish between the two subtypes and among strains of each subtype [6, 27, 51].

HSV-1 has a wide distribution, infecting over 3.7 billion adults by the age of 40. The prevalence of HSV-2 varies significantly and is influenced by factors such as geographic location, gender, and sexual behavior. Generally, women have higher rates of HSV-2 infection compared to men. Among populations with weakened immunity, such as individuals with HIV or attendees of STD clinics, as well as men who have sex with men (MSM), HSV-2 infection rates can exceed 80%. The prevalence of HSV-2 infection correlates with sexual activity, increasing with factors such as a higher number of sexual partners, younger age at sexual debut, and the presence of existing sexually transmitted diseases. In populations such as female sex workers, where near-universal infection rates are observed, rare genetic resistance to HSV-2 is suggested [9] (see Fig. 1 on cover II).

Transmission. Transmission of HSV most commonly occurs through close contact with an individual who is actively shedding the virus from a peripheral site, mucosal surface, or genital/oral secretions. In 1921, Lipschutz conducted experiments by inoculating material from genital herpetic lesions into the skin of humans, resulting in clinical infection

within 48 to 72 hours in six individuals and within 24 days in one case. It is now understood that infection occurs through the inoculation of the virus onto susceptible mucosal surfaces (such as the oropharynx, cervix, and conjunctivae) or through small breaks in the skin. Aerosol and fomite transmission of HSV are rare due to the virus's susceptibility to inactivation at room temperature and by drying. However, transmission of HSV-1 through orogenital contact is increasingly recognized, possibly due to a decrease in the age-specific prevalence of HSV-1 at the time of sexual debut. Certain occupations, such as dentists and respiratory care unit personnel, face the risk of spreading HSV-1 infection from oral secretions to other areas of the skin. Additionally, laboratory-acquired and nosocomial outbreaks involving hospital or nursery personnel have been documented. Herpes gladiatorum outbreaks among wrestlers are also well documented. Infants born to mothers shedding HSV at delivery can acquire the virus during birth. Anal and perianal infections with HSV-1 or HSV-2 are prevalent among sexually active MSM populations. Most cases occur within 5 days of contact, indicating the short incubation period of primary infection. However, the precise virologic determinants of transmission likelihood are not well understood. In the case of HIV infection, there is a clear relationship between genital and plasma HIV viral load and the per-coital risk for HIV transmission. However, because genital HSV-2 levels fluctuate rapidly over hours, both with and without therapy, the exact impact of source partner viral load during sex on the likelihood of transmission is uncertain. Nevertheless, modeling studies suggest that there is a certain viral load threshold that influences sexual transmission. Subclinical or asymptomatic shedding of HSV in oral and genital secretions is characteristic of infection in both immunocompetent and immunocompromised individuals, and transmission is more common during asymptomatic shedding. Prolonged episodes of asymptomatic shedding lasting several days have been well documented, even among immunocompetent patients who are taking daily antiviral therapy. In a prospective trial, the frequency of symptomatic recurrences poorly predicted the likelihood of transmission, underscoring the significant transmission risk associated with asymptomatic shedding. The frequency of detectable shedding varies widely among individuals who are seropositive for HSV-2, which likely contributes to the variability in reported rates of transmission per sexual encounter. DNA polymerase inhibitors, which reduce the frequency of asymptomatic shedding as well as the peak HSV-2 titers during recurrence, have been shown to decrease transmission within serodiscordant couples [9, 34, 54].

Clinical manifestations. Clinical manifestations of HSV infection vary depending on factors such as the site of infection, viral type (HSV-1 or HSV-2), and the host's age and immune status. The incubation period ranges from 2 to 12 days, with an average of around 4 days. Initial infections are generally more severe than recurrent ones. Orofacial infection, including gingivostomatitis and pharyngitis, is the most common initial manifestation of HSV-1, while recurrent lesions on the vermilion lip border (herpes labialis) are indicative of latent infection. Complications can include aseptic meningitis, transverse myelitis, sacral radiculopathy, and extragenital lesions during primary genital infection. HSV infection can also lead to esophagitis, pulmonary infections, hepatitis, and disseminated disease, particularly in immunocompromised patients, with severe skin infections observed in patients with eczema. Oropharyngeal HSV infection typically presents asymptomatically, but symptomatic cases may exhibit fever, oral lesions, sore throat, fetor oris, anorexia, cervical adenopathy, and mucosal edema. Genital HSV Infection: primary infections typically present with fever, malaise, myalgias, inguinal adenopathy, and signs of systemic illness. Other Primary HSV Skin Infections: atopic dermatitis can result in localized HSV skin infection known as eczema herpeticum, while trauma-induced cutaneous infection is termed herpes gladiatorum (wrestler's herpes or traumatic herpes). Ocular HSV Infection: manifestations include blepharitis or follicular conjunctivitis (keratitis and retinitis), progressing to dendritic lesions. Symptoms may include photophobia, tearing, chemosis, blurred vision, and preauricular lymphadenopathy. Central nervous system HSV Infection: characterized by headache, fever, behavioral disturbances, speech disorders, altered consciousness, and focal neurologic findings such as seizures. Neonatal HSV Infections: categorized into localized disease (affecting the skin, eyes, and/or mouth), encephalitis (with or without the involvement of skin, eyes, and/or mouth), and disseminated infection affecting multiple organs [13, 52].

Virus-Bacteria Interactions Pathophysiology

While bacteria and viruses often share similar habitats, the exploration of their potential collaboration in either promoting wellness or contributing to disease states has recently gained attention. Although some interactions between bacteria and viruses, such as those involving the influenza virus, have been well studied, researchers tend to prioritize understanding the location of infection over the mechanisms of cooperation. One of the most widely recognized examples of viral-bacterial synergy is the interaction between the influenza virus and *S. pneumoniae*. While an influenza virus infection alone can be severe, mortality rates significantly escalate with bacterial superinfections, as seen during the "Spanish flu" pandemic of 1918–1919, where millions of deaths were attributed mostly to second-

ary pneumococcal pneumonia. The mechanisms by which viruses influence bacterial colonization and invasion are diverse and multifaceted, involving both direct and indirect interactions that lead to disease. Direct interactions occur when viruses exploit bacterial components to facilitate their entry into host cells, primarily benefiting viral infiltration without conferring advantages to bacteria. In contrast, indirect interactions enhance bacterial pathogenesis as a consequence of viral infection, where viruses alter the host environment to make it more permissive for bacterial colonization. Enteric viruses predominantly utilize direct pathways, while respiratory viruses primarily exert their effects through indirect mechanisms. Although commensal bacteria inhabit various body systems, the respiratory and gastrointestinal microbiomes have been extensively studied. The gastrointestinal tract harbors a highly diverse bacterial population, with the oral cavity containing approximately 200 species and the distal intestine hosting up to 1000 species, reaching densities of up to 10^{14} bacterial cells per gram. In comparison, the respiratory tract contains a significantly lower bacterial load, with an estimated total of 10^4 bacteria and ample uncolonized space. Both commensal and pathogenic organisms colonize the nasopharynx, leading to infections in the upper and lower respiratory tracts when host homeostasis is disrupted [1, 25, 42]. Indirect interactions often involve four major mechanisms: (1) virus-induced upregulation of bacterial receptor concentrations on host cells, (2) virus-mediated damage to epithelial barriers, (3) virus-driven displacement of commensal bacteria, and (4) virus-induced suppression of the host immune response [35] (Fig. 2, cover III).

Bacterial species often benefit from viral infections. While viruses exist independently of proximal bacterial species, viral-induced disease states can create conditions where normally harmless bacteria become opportunistically pathogenic. In healthy circumstances, direct competition among microbes helps limit pathogen invasion by saturating colonization sites, bolstering barrier immunity to produce antimicrobials, and enhancing the immune response to invading microorganisms. However, when microbial populations are disrupted, previously inaccessible niches become available to invading pathogens, and surfaces where native microbiota once outcompeted disease-causing counterparts are compromised [22].

Viral propensity for Bacterial Adherence. The initial attachment of pathogens to mucosal surfaces is a crucial step in the development of respiratory diseases. Viral infections can alter the defense mechanisms of the host epithelium, potentially making it more susceptible to bacterial colonization. Studies in mice have indicated that this predisposition to bacterial attachment can occur not only during simultaneous viral-bacterial infections but also up to a week after initial viral infection or even after full recovery from influenza. Furthermore, the extent of interaction varies depending on the viral types and bacterial strains involved; only pneumococcal strains with high adhesive capacity were observed to adhere to human respiratory epithelium infected with adenovirus. This effect was primarily seen with adenovirus types known to cause respiratory disease in humans [2, 37].

Epithelial Barrier Disruption. The epithelial layer lining the respiratory tract mucosa serves as the primary defense against bacterial invasion. Any compromise in its barrier function can pave the way for pathogen entry. Viruses typically replicate within host cells, disrupting cellular processes, and leading to cell death either through metabolic exhaustion or direct lysis. Consequently, cell death can cause denudation of the epithelial layer, exposing the underlying basement membrane. *S. pneumoniae* has been observed to strongly bind to fibronectin, a protein prominently exposed at the basement membrane following epithelial denudation. Similarly, *Staphylococcus aureus* and *Moraxella catarrhalis* have demonstrated binding capabilities to extracellular matrix proteins, indicating potential benefits from virus-induced epithelial damage. Moreover, the binding efficiency of bacteria to fibronectin appears to be influenced by the amount and duration of fibronectin exposure. Viral presence can directly induce the upregulation of fibronectin expression, as demonstrated in rhinovirus infections, further facilitating pathobiont binding. Another consequence of epithelial disruption is the loss of epithelial integrity and the decreased inhibition of bacterial translocation. Studies have shown rhinovirus-induced paracellular migration of Haemophilus influenzae as a result of epithelial damage. Additionally, viruses may cause damage to ciliated cells, leading to reduced mucociliary velocity and impaired bacterial clearance [15, 39, 45].

Upregulation of Adhesion Proteins. Viral infections within cells can induce changes in the expression of antimicrobial peptides, such as defensins, which are crucial components of the innate immune system and directly combat pathogenic bacteria in the respiratory mucosa. Additionally, viral infections trigger a pro-inflammatory response leading to the upregulation of adhesion proteins in various cell types, including epithelial cells. These adhesion proteins serve as receptors that enable immune cells to bind to virus-infected cells and combat the viral invader. For instance, upon infection with viruses like respiratory syncytial virus (RSV) or para-influenza virus, eukaryotic cell surface receptors such as intracellular adhesion molecule 1 (ICAM-1), outer membrane protein P5-homologous fimbriae (P5 fimbriae), carcinoembryonic adhesion molecule-1 (CEACAM-1), and platelet-activating factor receptor (PAFr) are upregulated in different cell types. Several bacterial species can adhere to these adhesion proteins on the host cell surface. For example, rhinovirus-induced upregulation of ICAM-1 facilitates both its own invasion and the adhesion of *Haemophilus influenzae.*

Additionally, certain strains of *Streptococcus pneumoniae* and *Haemophilus influenzae* express phosphorylcholine, a natural ligand for PAFr, enabling them to attach to and invade host cells. The increased expression of PAFr in response to viral infection may thus enhance adherence to both *Streptococcus pneumoniae* and *Haemophilus influenzae*. However, influenza viruses may be an exception as *in vitro* studies have shown that they do not alter the expression of several receptors, including ICAM-1, CEACAM, and PAFr. Conflicting data exist regarding the potential role of PAFr in protecting against bacterial superinfection following influenza in mouse models, which may be attributed to strain-related differences and the timing and order of viral and bacterial exposure [21, 31, 37].

Viral Factor Production. In addition to direct interactions, the influenza virus can enhance bacterial adherence through alternative mechanisms, such as the production of neuraminidase (NA). NA, produced by influenza and parainfluenza viruses, facilitates bacterial entry into host cells by cleaving sialic acid residues, thereby exposing bacterial receptors on the surface of the upper respiratory tract. Numerous *in vitro* and animal studies, including those involving NA inhibitors, support this mechanism. While some bacteria, like *Streptococcus pneumoniae*, naturally express NA, their contribution to viral replication appears minimal due to their lower enzymatic activity and stricter binding requirements compared to viral NA. Conversely, respiratory syncytial virus (RSV) does not produce NA. Instead, bacterial adherence to RSV-infected cells is believed to be mediated directly by the expression of RSV-protein G. However, blocking G-protein activity only partially reduces excessive bacterial colonization in RSV-infected cells *in vitro*, suggesting an involvement of other mechanisms during viral-bacterial co-occurrence. These mechanisms may include the upregulation of additional receptors like ICAM-1 and PAFr or other indirect pathways [16, 20, 46].

Dysfunction of Immune System elements. In addition to facilitating the adhesion of neutrophils, monocytes, and other immune cells to virus-infected cells, viral-induced expression of the adhesion molecules may also promote the recruitment and activation of pro-inflammatory immune cells. However, respiratory viruses can directly impact the immune system by impairing neutrophil function, reducing oxidative burst, and accelerating neutrophil apoptosis, thus increasing susceptibility to bacterial superinfection. Certain strains of influenza virus may predispose to superinfection by *Staphylococcus aureus* due to ineffective recruitment and activation of natural killer (NK) cells. Furthermore, viral infection can alter monocyte function, leading to decreased surface expression of CD receptors. Additionally, viral presence influences the production and biological activity of cytokines. For instance, virus-induced interferon (IFN)-α and IFNβ can impair neutrophil responses by reducing the production of neutrophil chemoattractants. IFNγ downregulates macrophage activity, hindering bacterial clearance during the initial phase of infection. Blockage of IFNγ has been shown to decrease susceptibility to secondary bacterial pneumonia in mice. Moreover, the production of tumor necrosis factor (TNF)-α is downregulated during viral infection, potentially increasing susceptibility to secondary bacterial infections. Respiratory viruses can also interfere with Toll-like receptor (TLR) pathways, disrupting proper immune responses. This is exemplified by data from co-infection models with influenza virus and *Streptococcus pneumoniae* in mice, where excessive production of the immunosuppressive interleukin (IL)-10 following co-infection was associated with enhanced bacterial colonization and increased mortality. In recent years, there has been growing recognition of the potential involvement of viral and bacterial-viral interactions in the development of autoimmune diseases. Despite this, understanding the specific microbial contributions to autoimmunity remains a significant challenge, particularly in deciphering the role of commensal bacteria and chronic viruses. Establishing causality in these complex microbe-microbe interactions is further complicated by the intricate interplay between microbes and host genetics. Nevertheless, emerging research has highlighted the impact of microbial interactions on immune tolerance breakdown and autoimmune pathogenesis. Numerous human studies and animal models support the involvement of the microbiota in autoimmune disease development. While substantial progress has been made in elucidating host-pathogen interactions, establishing definitive causality in humans remains challenging. Molecular mimicry, leading to the loss of immune tolerance, has emerged as a key pathogenic mechanism in disease development. Future investigations will undoubtedly delve deeper into the dysregulation of crucial T-cell subsets implicated in autoimmunity, shedding more light on the role of chronic infections and commensal relationships. Advancements in sequencing technology and our understanding of the microbiota-host relationship are poised to drive further progress in unraveling these complex interactions [43].

Unilateral or Bilateral Synergy. While most studies emphasize a unilateral viral predisposition to bacterial colonization, there are indications that preceding bacterial infections may also increase susceptibility to subsequent viral infections. For instance, research has demonstrated that *H. influenzae* can induce the expression of ICAM-1 and TLR-3 on human airway epithelial cells, providing an entry point for rhinovirus. Similarly, human bronchial epithelial cells pre-treated with pneumococcus were found to be more susceptible to human metapneumovirus compared to those treated with other bacterial strains. Moreover, microbial interactions may disrupt the microbiota equilibrium,

creating opportunities for viral invasion and transmission. Recent studies have shown that the transmission of an enteric virus was less successful when the intestinal microbiota of mice were disrupted by antibiotic treatment. Additionally, viruses might exploit their microbial environment to evade immune clearance. However, limited information exists on bacterial predisposition to viral disease, warranting further research to elucidate the extent to which bacteria contribute to viral presence [19, 23, 48].

Viral-bacterial Interaction in Asymptomatic Individuals. Recent research suggests that asymptomatic individuals harboring viruses in the nasopharynx may play a role in bacterial colonization and sustained viral presence. Cohort studies involving asymptomatic children have revealed a positive association between the presence of adenovirus and rhinovirus and the colonization of *M. catarrhalis* and *H. influenzae.* However, the cross-sectional nature of most of these studies complicates the determination of a cause-effect relationship and the direction of these effects. To elucidate the sequence of observed effects, longitudinal studies with comprehensive follow-up during both health and disease states are warranted [4, 53].

Other Ways that Various Viruses Affect Bacteria. (A) When influenza A virus binds to bacteria, it boosts bacterial attachment to eukaryotic cells. (B) Multiple poliovirus virions binding to bacteria leads to increased coinfection and genetic recombination, giving rise to reassortant viruses. (C) Poliovirus binding to Lipopolysaccharides (LPS) enhances its affinity for poliovirus receptor (PVR), and the binding of human norovirus to bacterial histo-blood group antigens promotes infection. (D) Binding of gram-positive and gram-negative bacteria by picornaviruses and mammalian reovirus enhances virion thermostability [30].

Interactions between Herpes Simplex Virus and Bacterial Infections

Porphyromonas gingivalis and Dialister pneumosinte. Recent studies indicate that the progression of aggressive periodontitis, characterized by attachment, bone, and tooth loss, involves interactions among three herpes virus species (Epstein–Barr virus type 1 (EBV-1), human cytomegalovirus (HCMV), and HSV) and common periodontal bacteria, such as *Porphyromonas gingivalis* and *Dialister pneumosintes* [11, 36]. This synergistic relationship between herpesviruses and periodontal bacteria contributes to host immunosuppression, thereby promoting bacterial colonization and enhancing disease severity [18]. Additionally, periodontitis lesions may harbor HSV-1, human herpesvirus 6 (HHV-6), HHV-7, and HHV-8 in individuals infected with human immunodeficiency virus (HIV). Both HSV and HCMV infect various immune cells, inducing inflammation and cytopathic effects within host tissues, thereby compromising the host's defense against periodontal bacteria. Furthermore, viral proteins on infected host cells act as receptors for periodontal bacteria, while destroyed host cells offer attachment sites on exposed surfaces [10]. These lesions progress until rapid loss of connective tissue attachment and alveolar bone loss, hallmark features of periodontitis, occur. Hence, understanding the dynamic interplay between the immune system and virus-bacteria interactions is crucial for elucidating their pathogenic mechanisms [1]. In addition to the mentioned bacteria, herpesvirus-infected periodontitis lesions exhibit increased levels of periodontopathic bacteria such as *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Dialister pneumosintes, Prevotella intermedia, Prevotella nigrescens,* and *Treponema denticola* [40].

Enterococcus faecium. Enterococcus faecium is a Gram-positive bacterium found in the genus *Enterococcus.* While it can exist as a commensal organism in the gastrointestinal tract of humans and animals, it is also known to cause various infections, including endocarditis, urinary tract infections, prostatitis, intra-abdominal infection, cellulitis, wound infection, bacteremia, and neonatal meningitis [38, 50]. Several components present in the bacterial supernatant may contribute to its observed antiviral activity. One such group of proteinaceous molecules, called bacteriocins, exhibits antiviral properties. For instance, Enterocin CRL35, a bacteriocin produced by *Enterococcus faecium* CRL35, has been shown to reduce the replication of herpes simplex virus 1 and 2 by approximately 1 log10 *in vitro.* Studies suggest that this bacteriocin inhibits the synthesis of a viral glycoprotein necessary for viral infection and replication. The ability of enteric bacteria to bind to viruses, prevent their adherence to host cells, or inhibit various stages of the viral infection process may hold promise for therapeutic interventions [28, 49].

Streptococcus pneumoniae and Haemophilus influenzae. Studies examining the relationship between herpesvirus infections and bacterial infections, particularly involving *S. pneumoniae* and *H. influenzae*, have indicated a potential association. This association has been observed in cases of herpesvirus isolation occurring prior to (within 30 days), concurrently with (within seven days), and following bacterial infections caused by these pathogens. However, none of these associations have reached statistical significance. While there has been a longstanding clinical belief that pneumococcal pneumonia might trigger latent herpesvirus infections, recent clinical evidence has supported this notion. Nonetheless, it's important to note that fever itself can activate latent herpesvirus infections, and the specific contributions of the organism *(S. pneumoniae)* versus changes in the host environment (fever) are yet to be fully understood [41].

Lactobacillus crispatus. Lactobacillus crispatus is a rod-shaped species commonly found in the vagina and gastrointestinal tract, produces hydrogen per-

oxide, and plays a crucial role in protecting against urogenital pathogens. In a study assessing its potential antiviral activity against HSV-2 infection *in vitro*, *L. crispatus* was found to significantly reduce HSV-2 infectivity in the initial stages on both Vero and HeLa cell lines. Interestingly, the adhesion of lactobacilli to Vero cells was twice as strong as to HeLa cells, resulting in nearly 2.5 times higher protection of Vero cells against the virus. Co-incubation of HSV-2 with bacterial cells prior to virus inoculation also led to a significant decrease in virus titer. *L. crispatus* appears to inhibit viral entry into cells by trapping HSV-2 particles, and the formation of *L. crispatus* microcolonies on the cell surface may block HSV-2 receptors, thereby preventing viral entry into cells during the initial infection stages [29, 32].

Staphylococcus aureus. S. aureus along with herpes simplex virus type-1 (HSV-1) and type-2 (HSV-2), as well as *Candida albicans*, coexist in the oral and genital mucosa, yet their interaction remains poorly understood. Experimental reports indicate a significant decrease in HeLa-associated *S. aureus* levels for both HSV-1- and HSV-2-infected cells compared to virus-free HeLa cell controls. In contrast, HSV-1 and HSV-2 significantly enhance HeLa cell association of *C. albicans* yeast forms and germ tubes approximately two-fold each. This effect of *S. aureus* on germ tube and yeast form adherence to HSV-1- and HSV-2-infected cells is specific to the *Candida* phenotype tested. While HSV acts as an antagonist towards *S. aureus* adherence, it enhances *Candida* adherence. Moreover, the combination of the three pathogens results in *S. aureus* adherence that is either unaffected or partially restored depending on both the herpes viral species and the fungal phenotype present. These studies highlight the ability of HSV to regulate the adherence of multiple opportunistic pathogens within the inter-kingdom microbiome. It suggests that HSV-1 and HSV-2 modulate both fungal and bacterial adherence to cells, likely in part through HSV-mediated alteration of heparan sulfate cell surface display. These findings signal a shift in perspective from the conventional notion that host factors exclusively govern microbiome composition, to one where a lifelong latent viral pathogen could influence the host through specific molecular mechanisms that alter biofilm initiation. This suggests a usurpation of regulatory control over microbiome membership. Further investigations are warranted to delineate the precise role of various HSV viral entry receptors in modulating staphylococcal and candidal adherence. Understanding the initial interactions between HSV-1 and HSV-2, as permanent members of the host microbiome, and chronic colonizers like *S. aureus* and *C. albicans*, opens up new possibilities for biofilm inhibition and eradication. Additionally, in another study, positive cultures of *Staphylococcus aureus* were more frequently reported in burn patients with herpes infection [44].

Acinetobacter baumannii. In one study, HSV activation was linked to prolonged hospital stays and mechanical ventilation. Moreover, HSV activation raised the likelihood of acquiring positive pulmonary cultures for *Acinetobacter baumannii* and methicillin-resistant *Staphylococcus aureus* in wound cultures. It also heightened the risk of positive cultures for any strain of *A. baumannii*. Severe burn injury patients experiencing HSV activation exhibited prolonged mechanical ventilation and hospitalization periods, along with an elevated susceptibility to infections from opportunistic bacteria [44].

Group B Streptococcus (GBS). Studies indicate GBS colonization as a risk factor for genital tract shedding of HSV-2 in women. While vaginal GBS colonization is common, even modest associations with HSV-2 shedding can result in significant risks for virus transmission. GBS is generally considered as a microorganism that does not provoke a substantial host inflammatory response when present in the vagina. Its detection usually signifies colonization rather than infection, as it's not typically linked to vulvovaginal symptoms. However, pregnant women with heavy vaginal GBS colonization during mid-gestation face a significantly higher risk of delivering a preterm, low-birth-weight infant compared to those with either no or light GBS colonization. This observation suggests that although vaginal GBS colonization may not cause evident vulvovaginal symptoms, it could induce alterations in the vaginal microenvironment, with heavier colonization potentially more prone to trigger such changes [8].

Ventilator-associated pneumonia (VAP). Herpes simplex virus (HSV) shedding in lower respiratory tract (LRT) secretions is not uncommon in cases of VAP, and it correlates with increased severity and a poorer prognosis. In a study involving 177 patients with confirmed bacterial VAP, HSV was detected in 13.4% of cases. Patients with HSV shedding exhibited more severe underlying conditions and experienced worse outcomes. They required more antibiotics for the VAP episode, had a higher incidence of *Clostridium difficile* infection, spent a longer duration on mechanical ventilation, had extended stays in the intensive care unit and hospital, and had higher mortality rates compared to those without HSV shedding [5].

Bacterial urinary tract infections (UTIs). UTIs typically involve bacteria such as *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. The underlying mechanisms involve the release of chemokines and cytokines, including CXCL8, CCL2, interleukins (IL-6, IL-8, IL-10, IL-17A), and granulocyte colony-stimulating factor (G-CSF) [26]. In certain investigations, pre-infection of HT-1376 cells with HSV-2 led to a tenfold increase in adherence of an *E. coli* strain (U1), isolated from a patient with severe hemorrhagic cystitis. Conversely, in HSV-2 pre-infected cells, the number of *C. trachomatis* inclusion bodies was significantly reduced [44].

Bacterial vaginosis (BV). Diagnosis of BV may correlate with an elevated risk of acquiring HSV-2 infection in the population [8]. HSV-2 infection stands as a significant risk factor for BV. Pharmacological suppression of HSV-2 may potentially decrease both the incidence of BV and BV-associated complications. Observations recognize a heightened risk of HSV-2 acquisition among women with BV, mirroring the association previously noted between BV and HIV. Given the widespread prevalence of BV and the persistent nature of HSV-2 infection, widespread screening and treatment of BV might offer an avenue to mitigate the incidence of HSV-2 infection in women. Further research is necessary to ascertain whether screening and treating BV could diminish susceptibility to HSV-2 acquisition in women [12].

Human immunodeficiency viruses. HSV-2 infection escalates the susceptibility to HIV acquisition. The prevailing HSV-2 infection correlates with a three-fold rise in the risk of HIV acquisition among both genders in the general populace. This suggests that in regions with high HSV-2 prevalence, a significant portion of HIV cases could be attributed to HSV-2. This discovery bears crucial implications for managing individuals diagnosed with HSV-2 infection, especially those who are newly diagnosed. Interventions aimed at HSV-2, such as novel HSV vaccines, hold promise for additional protection against HIV, particularly in areas with high rates of co-infection [14, 24].

HSV prevention

Prophylaxis against Herpes Simplex Virus (HSV) remains a challenge due to the lack of a licensed vaccine for HSV-1 or HSV-2. Previous studies investigating vaccines targeting glycoprotein D (gD2) and/or glycoprotein B (EB1) were discontinued due to inconsistent results. However, understanding the factors associated with HSV protection is crucial for vaccine development. In terms of exposure prophylaxis, symptomatic relief during acute illness is paramount and typically involves antiviral therapy, pain relief, sitz baths, and lesion drying. Effective counseling strategies are essential, particularly for asymptomatic patients identified through serologic testing. Recognition of subtle genital ulcers is emphasized, and various printed materials aid in counseling sessions. Prevention strategies focus on serodiscordant relationships and include measures such as full disclosure, condom use, abstinence during symptomatic periods, and antiviral therapy. Valacyclovir, administered at a dose of 500 mg daily, has been shown to reduce transmission by 50% and serves as a primary prevention method, albeit imperfect. Moreover, considering asymptomatic transmission is crucial, highlighting the necessity for comprehensive prevention strategies [17].

Conclusion

The interplay between viral and bacterial pathogens presents a complex and multifaceted dynamic in human health. From facilitating bacterial colonization to modulating immune responses, viruses can significantly impact the outcome of bacterial infections and vice versa. This intricate relationship extends across various microbial ecosystems, from the respiratory tract to the urogenital system. Moreover, the bilateral interactions between viruses and bacteria underscore the importance of considering both pathogens in clinical diagnosis, treatment, and prevention strategies. Furthermore, the implications of these interactions extend beyond individual infections to influence broader health outcomes. For instance, the HSV virus can have a two-way relationship with different mechanisms on various bacterial infections throughout the body and affect the severity and prognosis of infectious diseases. Overall, understanding the complex interplay between viruses and bacteria offers insights into disease pathogenesis, diagnostic strategies, and therapeutic interventions. Further research in this field holds promise for advancing our understanding of microbial dynamics and improving clinical outcomes in infectious diseases.

Additional information

Conflicts of interest. The author declares that there are no conflicts of interest.

Funding. N/A.

Acknowledgments. N/A.

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Поступила в редакцию 30.07.2024
Отправлена на доработку 18.02.2025
Принята к печати 25.03.2025

Received 30.07.2024
Revision received 18.02.2025
Accepted 25.03.2025

Иллюстрация к статье «Взаимодействия между вирусными и бактериальными патогенами в развитии инфекций: обзор с акцентом на вирус простого герпеса» (авторы: М.Х. Калантар Нейестанаки, А. Мехдипур) (с. 465–475)

Illustration for the article “The interaction between viral and bacterial infections: a comprehensive review focusing on Herpes Simplex Virus (HSV)” (authors: Kalantar Neyestanaki M.H., Mehdipour A.) (pp. 465–475)

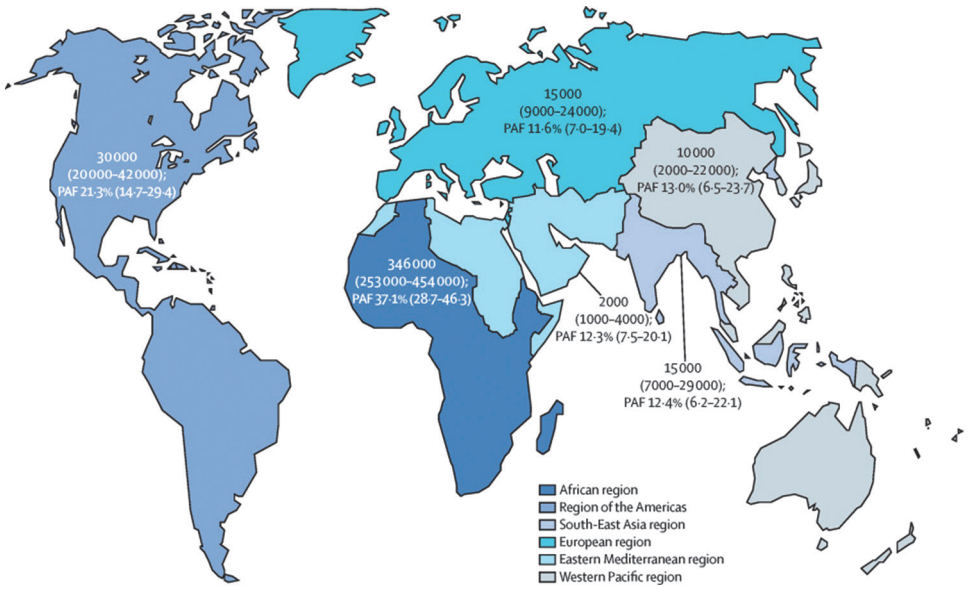

Figure 1. The global prevalence of HSV-2 across different geographic regions [24]

Иллюстрация к статье «Взаимодействия между вирусными и бактериальными патогенами в развитии инфекций: обзор с акцентом на вирус простого герпеса» (авторы: М.Х. Калантар Нейестанаки, А. Мехдипур) (с. 465–475)

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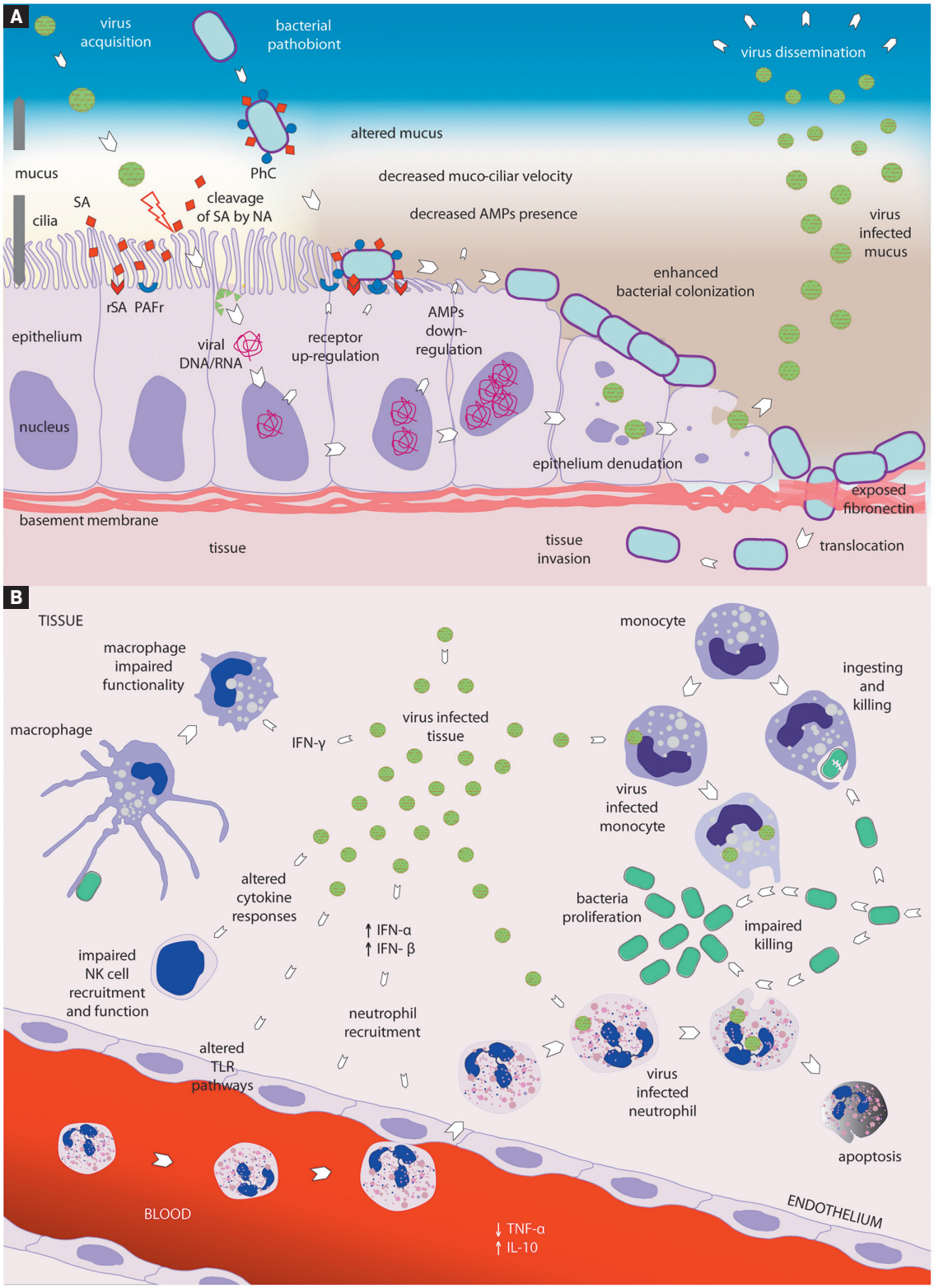

Figure 2. Two main aspects of viral-bacterial interactions

Note. (A) Interaction on the respiratory epithelial surface: Viruses can make the respiratory tract more vulnerable to bacterial colonization by damaging mucosal surfaces, reducing ciliary function, and compromising epithelial integrity. Infected cells may also decrease antimicrobial peptide expression and expose bacterial receptors through neuraminidase activity. Additionally, viruses can directly or indirectly enhance bacterial colonization by upregulating receptors required for bacterial adherence. (B) Interaction with the host immune system: Viral infections can alter immune function, favoring bacterial invasion. This includes reducing the recruitment and functionality of NK cells and impairing neutrophil recruitment and function. Viral-induced interferons may also affect macrophage activity and decrease pro-inflammatory cytokine levels, leading to impaired immune responses to bacterial infections [4].