MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Otolaryngology Open Access Journal
ISSN: 2476-2490

COVID-19-Challenges but also Benefits

Avramov T*

Department of ENT Clinic, Medical University, University Hospital "Tzaritsa Yoanna-ISUL", Bulgaria

***Corresponding author:** Toma Avramov, Department of ENT Clinic, Medical University, University Hospital "Tzaritsa Yoanna-ISUL", 8 Bjalo More str, Sofia 1508, Bulgaria, Tel: +35929432563; Fax +35929432521; Email: toma_avramov@abv.bg

Conceptual Paper

Volume 9 Issue 1

Received Date: December 18, 2023

Published Date: January 18, 2024

DOI: 10.23880/ooaj-16000281

Abstract

Introduction: The COVID-19 pandemic has changed the way we live and put health systems and economics around the world under stress. It caused about 598 million cases and resulted in about 6.4 million deaths worldwide.

In recent decades, we have seen extraordinary progress in the field of biomedical knowledge as well as in the study of emerging new viral pathogens. New outbreaks of infection in different geographical areas have led to the isolation of a large number of highly pathogenic viruses belonging to the families Filoviridae, Arenaviridae, Bunyaviridae, Paramyxoviridae, Coronaviridae, Flaviviridae, Togaviridae and Hepeviridae, which have a zoonotic origin. Zoonoses are diseases transmitted from animals to humans and pose a serious threat. The development of protective and therapeutic measures against the spread of SARS-CoV-2 is an important part of tackling the problem, but only when we clarify the interrelationship in the interaction between viral and bacterial pathogens, the human microbiota, immunity and our way of life.

Conclusion: Infectious diseases are among the strongest causes of selective pressures driving human evolution. Understanding the possible interactions between viral and bacterial pathogens on the one hand and the human microbiota and genome will allow us to correctly use pharmacological, non-pharmacological and dietary interventions to predict and control the risk in the course of such diseases. Genetics in the coming decades will likely allow us to identify loci characterizing the genetic variation of immune-related genes to understand the dynamics of human immunity formation. Adopting a One health approach to public health is of great importance. The human population is only a small, albeit important, part of the Earth's ecosystem. The relationship between human health and animal health must be taken into account, as was suggested to us during the last pandemic.

Keywords: SARS-COV-2; Zoonoses; Prebiotics; Probiotics; Prevention; Interactions; Cocirculating Pathogens; Microbiota; Human Genom

Abbreviations: HA: Hemagglutinin Esterase; HMPV: Human Metapneumovirus; HRV: Human Rhinovirus; IAV: Influenza A Virus; IBDV: Infectious Bursal Disease Virus; ICIs: Immune Checkpoint Inhibitors; IFN: Interferon; ISG`s: Interferon Stimulated Genes; LEV: Live Enterovirus Vaccine ; MDCK: Madin-Darby Canine Kidney Cells; MERS-COV: Middle East Respiratory Syndrome Coronavirus; NDV: Virulent Newcastle Disease; OS: Overall Survival; PFS: Progression Free Survival; RSV: Respiratory Syncytial Virus; SARS-COV: Severe Acute Respiratory Syndrome Coronavirus.

Introduction

The COVID-19 pandemic has changed the way we live and put health systems and economics around the world under stress. It caused about 598 million cases and resulted in about

6.4 million deaths worldwide [1]. At the beginning of the pandemic, most of us accused the health care system of being slow, clumsy, and even incompetent in directing resources. Despite the effectiveness of vaccines, the circulation of SARS-CoV-2 remains constant, suggesting the impossibility of its elimination and a transition to endemic or seasonal dynamics. The difference in excessive expectations for them and the real possibilities of vaccination has led to "fatigue" in the confidence in vaccines. It was much easier to explain that, apart from the undoubted benefits of vaccination, side effects and complications can be seen in a negligible percentage of recipients, and that the non-responders rate can be as high as 5%. With coronaviruses, there is a constant emergence of new variants, which will likely lead to adjustments, like with the flu vaccine every year. Separately, the need to develop a strategy was seen in the use of pharmacological, non-pharmacological and dietary interventions for predicting and controlling the risk in the course of such diseases. These interventions can only be successful if we understand the possible interactions between viral and bacterial pathogens and the human microbiota and genome. Coronaviruses belong to the group of respiratory viruses. Those of them that most commonly attack the human respiratory tract are: influenza virus, parainfluenza virus, respiratory syncytial virus (RSV), adenoviruses, measles virus, rhinoviruses, and coronaviruses [2]. Before the COVID-19 infection caused the global pandemic in 2020, coronavirus diseases were primarily of veterinary interest. Before it, humanity faced other pandemics caused by viral pathogens. These are: the "Spanish flu" at the beginning of the twentieth century (1918-19), which caused about 40 million deaths, the "Asian flu" in 1957, the "Hong Kong flu" in 1968 with documented about 3 million deaths, 2002/ 2003 the coronavirus causing acute respiratory syndrome (SARS-CoV), 2009 the "swine flu" and in 2013 the "bird flu" (H7N9) and MERS-CoV [3-7].

Infectious diseases are among the strongest causes of selective pressures driving human evolution. In recent decades, we have seen extraordinary advances in biomedical knowledge, including in the study of emerging viral pathogens. All of them have a zoonotic origin. Zoonoses or diseases of animal origin are diseases transmitted from animals to humans and pose a major threat to human health and life. Animals are often asymptomatic carriers of pathogens and spread them in the environment with their excreta.

Zoonoses are defined as diseases transmitted between animals and humans as a result of direct contact, indirect contact with the environment or through food [8]. Among recognized pathogens causing human disease, almost 60% are zoonotic infectious agents and up to 75% of "emerging" human pathogens. Of the known viruses that infect humans, about 80% persist in "non-human reservoirs", which are most often farm animals and birds, domestic animals and birds, and to a lesser extent animals, birds and arthropods in the wild. Today, from the 1,400 pathogens that cause human disease, 800 are of animal origin [9,10].

The key to unraveling the emergence and/or re-emergence of viral pathogens is the host-pathogen-environment interrelationship. Modes of transmission include direct contact, skin abrasions and injuries, bites, through food, soil and water. Sometimes the same infection can be transmitted in several ways. Ticks, fleas, mosquitoes, arthropods and rodents can be mentioned as vectors for their transmission. Shepherds, farmers, zookeepers, hunters, slaughterhouse workers and veterinarians are most commonly affected [3,11].

Viral pathogens adapted to the human population are divided into DNA and RNA viruses. DNA viruses are thought to have evolved and diversified over millions years [2,12]. RNA viruses probably have a more recent evolution and have adapted to the human population in only about 1000 years. According to the studies, 158 species were found in RNA viruses, divided into 47 genera and 17 families, in contrast to DNA viruses, where 91 species were found, divided into 22 genera and 8 families. Nevertheless, in the latter 87% have adapted to humans, while in RNA viruses only a small proportion have so far adapted [13]. Some of them may circulate asymptomatically until their new clinical manifestations are detected [14]. The origin of most human viruses is unknown, but the majority of them can be categorized as "crowd diseases", which require a relatively high population density to stabilize [3,15]. The composition of the virus pool is dynamically changing. Over time, some virus species tend to disappear while others thrive in their natural hosts. Most often, new species arise as a result of jumping from one host to another, crossing the species barrier. In this case, we are just "accidental" hosts, but only a small part of these viruses are able to persist in certain human populations (endemics) or spread between different populations (epidemics) [16]. The last pandemic required the development of measures both to control and protect against the spread of SARS-CoV-2, but also to deal with new similar challenges. All these measures will be half-hearted if the interactions between circulating viral and bacterial pathogens are not studied and understood. Nonpharmacological interventions used during the pandemic also have an impact on these interactions. First of all, we must determine which interactions are synergistic or antagonistic, according to their nature - short-term or long-term, and whether the interaction changes the individual's susceptibility to infection and the severity of the course. In this complex equation, the factors determining the susceptibility of the person (the host) must also be introduced to infection – age, health status, diet, exposure to the pathogen, co-infection, current state of the

individual's immunity and genome. We must not forget about their synergistic or antagonistic interactions with the human microbiota. Differences in emerging and re-emerging infections should also be considered. When pathogens are introduced into new geographic areas, explosive epidemics are usually observed, followed by declining incidence rates. When the jump to man is localized as a result of climatic or social changes, the incidence shows successive increases.

Co-circulation of viral pathogens can lead to multi-epidemics such as COVID-19, RSV and influenza. Elucidating the potential interactions of viral pathogens both with each other and with bacterial pathogens will help us better predict and control risk in such multi-epidemics [15,16]. At the same time, recent viral infections may induce a refractory period during which the host is unlikely to be infected by another respiratory virus. It is important that viruses share the same environmental conditions – for example, cold weather. Factors that would point us toward viral interference are: a) the ability of the interfering virus to induce a rapid IFN response, b) the degree of sensitivity of the second virus to immune mediators, c) the degree to which different viruses counteract the induction and antiviral effects of IFN and e) the pattern of virus-induced innate immune response in the upper and lower respiratory tract [17].

The concept of viral interference was first introduced by Voroshilova et al. in the 60s of the 20th century.

The likely mechanism is the interferon response, which provides temporary non-specific immunity to the host [18]. The group is developing live enterovirus vaccines (LEV) from attenuated enteroviruses for the prevention of enteric disease due to unrelated enteric pathogens in children. Apart from the protective effect of LEV against pathogenic enteroviruses, particularly polioviruses, oral administration of LEV in children reduced the detection of some unrelated respiratory viruses—influenza, parainfluenza virus, RSV, HRV, and human adenovirus. We will have to answer whether SARS-CoV-2 does not cause the same effect in the above-mentioned respiratory viruses. This effect suggests the phenomenon of viral interference [19]. During the same annual period, several respiratory viruses may circulate simultaneously. They can simultaneously or sequentially infect the respiratory tract and cause virus-virus interaction. Depending on whether the infection of the first virus will enhance or reduce the infection and replication of the second virus, we observe a positive (synergistic) or negative (antagonistic) interaction. A positive interaction or co-infection leads to increased disease severity – for example, SARS-CoV-2 and the pandemic influenza virus A(pH1N1) pdm09 [20]. The negative virus-virus interaction is homologous and heterologous depending on whether viruses belong to the same or to different families. In the homologous interaction, presumably cross-reactive immunity against the first virus prevents infection by the second virus (for example, between different subtypes or lineages of influenza - H1N1, H3N2 and pH1N1. In the heterologous type of interference, the induction of the nonspecific immune response by the first virus reduces or prevents the infection and replication of the second virus (e.g. influenza virus A - IAV and RSV) [21-23]. The likely mechanism of the negative virus-virus interaction is the induction of transient innate immunity by the interfering virus. Structural elements of viruses are recognized by receptors on epithelial and immune cells. Recognition triggers the expression of interferon (IFN)-stimulating genes (ISGs) type I (IFN-α/β) and type III (IFN-λ). The IFN-α/β receptor is expressed in most cell types, while IFN -λ occurs primarily in epithelial cells of the gastrointestinal and respiratory tract Secreted IFNs bind to receptors on the surface of infected and neighboring cells to enhance ISG expression. Viral defense is expressed in the production of effectors that directly inhibit viral replication, as well as chemokines and cytokines [24]. The study of viral interference is also particularly important in view of the mechanisms used by respiratory viruses to counteract the induction and antiviral action of IFN, which may influence the type of virus-virus interaction. Influenza viruses and SARS-CoV-2 exhibit a wider range of ways to evade IFN induction and signaling than RSV, human Metapneumovirus (HMPV) and human rhinovirus (HRV). Blockade and/or reduction of cell surface receptors and competition for cellular resources are considered mechanisms of negative virus-virus interaction. Examples of such interaction are: expression of neuraminidase in 293T cells infected with influenza A(H1N1) or A(H3N2) preventing subsequent infection with retroviruses or second IAV by removing sialic acid from the cell surface and inhibiting RSV replication during of IAV coinfection in MDCK cells through competition for viral protein synthesis [25,26]. A positive virus-virus interaction is the effect of human parainfluenza virus type 2 to enhance the growth of IAV in Vero cells. Co-infection can increase the severity of disease by excessive production of IFN or pro-inflammatory cytokines or by reduced secretion of non-inflammatory mediators such as interleukin (IL)10 [27]. Studying the types of interference in animal models has a potential limitation because the immune response against human respiratory viruses and immune evasion mechanisms in most cases differ. The introduction of non-pharmacological interventions should be carefully fine-tuned in order not to lose some natural allies during epidemics/pandemics as the seasonal viral circulation changes.

Potential viral interferences are important in the context of elucidating their possible cooperation with some bacterial pathogens, allowing prediction of more severe respiratory diseases. This would help us better control both the risk and the therapeutic approach in these patients. The interactions can be divided into three types: a) the virus potentiates

bacterial colonization, b) the proteases of the respiratory tract bacteria induce conformational changes leading to increased pathogenicity and tissue tropism of the virus, and c) the bacteria enhance viral infection by activating proteases of the host [28-31].

Bacterial pathogens that are most often found in the respiratory tract are: Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenza, Staphylococcus aureus, Neisseria meningitidis, Mycobacterium tuberculosis, Bordetella pertussis and, in immunocompromised patients, Pseudomonas aeruginosa [32]. To cause disease, microorganisms must colonize mucosal surfaces, penetrate tissues and initiate growth, inhibit the patient's defense mechanisms, and cause damage to the host. Bacterial colonization of airway surfaces occurs more readily when mucociliary clearance is impaired by a previous viral attack, but bacterial lung infection is more common in primary ciliary dyskinesia [33]. RSV has been found to cause loss of cilia in human bronchial cells in vitro, and influenza virus has been shown to cause damage to the ciliar epithelium and the bronchial epithelial lining [34,35]. The virus-induced change in the membrane potential of the host cells is considered the most likely reason for the increased bacterial adhesion. Viral glycoproteins expressed on host cell membranes can be receptors for bacteria. A study shows that influenza virus hemagglutinin (HA) on infected MDCK cells acts as a receptor for group B streptococci. In more recent studies, the change in the glucoconjugate structure of murine nasopharyngeal mucosa caused by influenza infection is associated with changes in patterns of lectin binding [36,37]. A possible mechanism for adherence of staphylococci to virus-infected cells in vivo is thought to be that infected cells may be coated by a viral antibody that serves as a receptor for staphylococcal protein A. The damage to epithelial cells resulting from infection with influenza virus helps to penetrate the tissues. Staphylococci seem to attack only those parts that are damaged by the virus. Damage to the respiratory epithelium by other viruses may also have a similar effect [38,39]. Viral infection can inhibit the host's defense mechanisms against bacterial attack – nonspecific humoral factors, nonspecific phagocytosis by neutrophils and macrophages early in the infection, and a later immune response mediated by a specific antibody. In human neutrophils after interaction with influenza virus in vitro, reduced chemotaxis and phagocytic activity were observed when interacting with staphylococci [40]. The mechanism of reduction of the bactericidal power of neutrophils and macrophages after influenza virus infection is expressed in disruption of lysozyme production by both types of phagocytes [41,42].

The influenza virus is the most studied example of a positive cooperation between a virus and bacteria. Influenza primarily causes upper respiratory tract infections, but when the lungs are affected it can be fatal due to pulmonary edema and hemorrhage. However, most deaths during influenza epidemics are due to secondary bacterial infections. Most often they are caused by: Streptococcus pneumoniae, Haemophilus influenza, Staphylococcus aureus and Neisseria meningitidis. Influenza, pneumococcal infection and meningococcal disease have a seasonal relationship, manifesting in the winter months [2,43-47]. RSV and human parainfluenza virus also have similar interactions with Streptococcus pneumoniae [43,48,49]. Unlike most respiratory viruses, rhinoviruses and seasonal coronaviruses (HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1) appear to act independently [50]. We have yet to elucidate in SARS-CoV-2 the possible positive cooperation with bacterial pathogens. Proteases of respiratory tract bacteria can induce cleavage of influenza virus HA in vivo. This was first found for the protease of Staphylococcus aureus and then for those of other bacteria in the respiratory tract, such as Streptomytes griseus Aerococcus viridans. Cleavage of HA from S. aureus and A. viridans not only confers virus infectivity and replication capacity in vitro, but also increases virus replication and pathogenicity in mice [51-54]. Bacteria of the respiratory tract may be able to enhance influenza infection by activating host proteases causing cleavage of HA leading to increased pathogenicity of the virus. It is assumed that these are staphylokinase, streptokinase and others, facilitating the cleavage of HA by generating plasmin from plasminogen [31,52]. Cooperation between viruses and bacteria can cause respiratory diseases that are more severe than those caused by either pathogen alone. This is also due to the fact that the majority of deaths during influenza epidemics are due to secondary bacterial infections [43-47].

The human microbiota consists of 39 to 44 billion microbes, about ten times the number of cells in our body. The microbiome is estimated to have 8 million genes compared to 20-25,000 human genes. Probiotics are defined by Fuller, et al. as live organisms that, when ingested in sufficient quantities, can alter the gut microbiota and stimulate the immune system after ingestion. Their main properties include acid resistance, strain specificity, lack of side effects, reduction of pathogenic microbial numbers and viability during storage. The human microbiota performs a barrier function on the epidermis, mucous membranes, gastrointestinal tract, lungs and urogenital system. The gut is supposed to be the most dysbiosis and is associated with various pathologies, including cancer. In a healthy gut microbiome, or eubiosis, bacteria are involved in preventing infections, breaking down food, synthesizing vitamins, regulating gut and brain function, and modulating the immune system. Disruption of the function of the immune system, which plays an important role in homeostasis, leads to imbalance, disease and increased risk of cancer.

The microbiota locally and systemically influences the immunomodulatory functions - reduction of inflammation, anti-tumorgenesis and suppression of tumor growth and improvement of the intestinal barrier. Bacteria also play the role of modulators, promoting or disrupting immunological functioning by interacting with specific immune receptors. In dysbiosis and carcinogenesis, the protective immunomodulating functions are turned off. The benefit of probiotics for overall health is expressed in competitive inhibition (they compete with pathogenic bacteria for access to nutrients and limit their colonization in the intestine), production of antibacterial substances and organic acids, immunomodulatory properties, improvement of protein and mineral absorption and regulation of homeostasis of the gut microbiota [55-59].

Unfortunately, there are more avian and animal models in studying the action of probiotics. A study of the potential benefits of using Bacillus subtilis as a probiotic in broilers found the following effects on intestinal morphology and microbiota. In the histomorphology of the gastrointestinal tract, there is an increase in the height of the villi, a decrease in the depth of the crypts and a greater ratio of the first two in the jejunum and ileum, leading to improved absorption of nutrients. In the intestinal microbiota, probiotics affect its composition and activity and to limit colonization with pathogenic microorganisms. Possible mechanisms include reduction of gastrointestinal pH, modulation of the immune system, and production of organic acids. Separately, improvement of the integrity of the intestinal barrier, enhanced immunogenicity and correction of microbial signaling pathways in the cells of the intestinal epithelium were observed [60,61]. Qiu found that dietary supplementation of Bacillus subtilis significantly increased Lactobacillus and Bifidobacterium counts in the ileum and cecum, and decreased coliforms and Clostridium perfringens in the cecum. Studies of the effect of probiotics against Newcastle disease virus (NDV) and infectious bursal disease virus (IBDV) have shown that they increase the titer of specific antibodies to these viruses. Prevention and reduction in severity of NDV and IBDV infections was observed. Probiotic supplements significantly enhance the immune response of broilers by increasing antibody production and improving gut integrity, reducing local inflammation and restriction of bacterial translocation. This leads to improved protection against viral and bacterial agents. This proves that probiotic supplementation is a dietary intervention improving humoral immunity in broilers compared to this unsupplemented group [62,63].

Studies performed in mouse models show disruption of the microbial system of the gastrointestinal tract during antibiotic therapy. This may have a significant effect on the patient's response to immunotherapy for malignancy, but a similar effect on the immune response to viral and bacterial pathogens cannot be excluded. Taking an antibiotic shortly before or after initiation of immune checkpoint inhibitors (ICIs) therapy significantly affected overall survival (OS) and progression-free survival(PFS). In this case, taking prebiotics is more appropriate. During digestion, prebiotics are broken down into short-chain fatty acids by bacterial enzymes and support the growth of certain microbiota [64].

Conclusion

Infectious diseases are among the strongest causes of selective pressures driving human evolution. Conducting research on emerging human-adapted viruses should not remain at the level of knowledge of pathogen biology, but to be introduced to clinicians. This will reduce the possibility that these etiological agents remain unidentified, infect human populations, and only when they cause epidemics/pandemics will the potential of health systems be mobilized. While the COVID-19 pandemic has changed the way we live and stressed health systems and economics around the world, it has also had tangible benefits. Adopting a One health approach (Sorice A.) to public health in the future will be of great importance. The human population is only a small, though important, part of the Earth's ecosystem. The relationship between human health and animal health must be taken into account, as was suggested to us during the last pandemic.

Understanding the possible interactions between viral and bacterial pathogens on the one hand and the human microbiota and genome on the other will allow us to predict the likely course of infection. It will also enable us to properly combine pharmacological, non-pharmacological and dietary interventions and control the risk of developing such diseases. However, studying interference types in animal models has a potential limitation because the immune response against human respiratory viruses and immune evasion mechanisms in most cases differ. Proper use of dietary interventions (prebiotics, probiotics and agents) to block receptors on mucosal epithelial cells used by pathogens will likely allow to reduce their spread between individuals and limit pharmacological interventions.

References

1. WHO (2022) Weekly epidemiological update on COVID-19–31 August 2022. pp: 1-11.

2. Mahy BWJ, Collier L (1998) Topley and Wilson's Microbiology and Microbial Infection. In: 9th (Edn.), Virology, Arnold, London, United Kingdom.

3. Parvez MK, Parveen S (2017) Evolution and emergence of

patogenic viruses: Past, present and future. Intervirology 60(1-2): 1-7.

4. Wever PC, Bergen LV (2014) Death from 1918 pandemic influenza during the First World War: a perspective from personal and anecdotalevidence. Influenza Other Respir Viruses 8(5): 538-546.

5. Dawood FS, Iuliano AD, Reed C, Meltzer MI, Shay DK, et al. (2012) Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. Lancet Infect Dis 12(9): 687-695.

6. WHO (2003) Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003.

7. Lu S, Xi X, Zheng Y, Cao Y, Liu X, et al. (2013) Analysis of the clinical characteristics and treatment of two patients with avian influenza virus (H7N9). Biosci Trends 7(2): 109-112.

8. European Food Safety Authority (EFSA) (2016) European Centre for Disease Prevention and Control (ECDC). The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2015. EFSA J 14: e04634.

9. Zhang HL, Mnzava KW, Mitchell ST, Melubo ML, Kibona TJ, et al. (2016) Mixed Methods Survey of Zoonotic Disease Awareness and Practice among Animal and Human Healthcare Providers in Moshi, Tanzania. PLoS Negl Trop Dis 10(3): e0004476.

10. Lee G, Schafer AI (2012) Cecil Medicine. In: 24th (Edn.), WB Sounders, Philadelphia, PA, USA, pp: 1964-1967.

11. Chikeka I, Dumler JS (2015) Neglected Bacterial Zoonoses. Clin Microbiol Infect 21(5): 404-415.

12. Simmonds P (2001) Reconstructing the origins of human hepatitis viruses. Phil Trans R Soc Lond B 356(1411): 1013-1026.

13. Woolhouse MEJ, Adair K (2013) The diversity of human RNA viruses. Future Virol 8(2): 159-171.

14. Shukla P, Nguyen HT, Torian U, Engle RE, Faulk K, et al. (2011) Crossspecies infections of cultured cells by hepatitis E virus and discovery of an infectious virushost recombinant. Proc Natl Acad Sci USA 108(6): 2438-2443.

15. Wong A, Barrero Guevara LA, Goult E, Briga M, Kramer SC, et al. (2023) The interactions of SARS-CoV-2 with cocirculating pathogens: Epidemiological implications and current knowledge gaps. PLOS Pathogens 19(3): e1011167.

16. Kitchen A, Shackelton LA, Holmes EC (2011) Family level phylogenies reveal modes of macroevolution in RNA viruses. Proc Natl Acad Sci USA 108(1): 238-243.

17. Piret J, Boivin G (2022) Viral Interference between Respiratory Viruses. Emerging Infectious Diseases 28(2): 273-281.

18. Voroshilova MK (1989) Potential use of nonpathogenic enteroviruses for control of human disease. Prog Med Virol 36: 191-202.

19. Chumakov MP, Voroshilova MK, Antsupova AS, Boĭko VM, Blinova MI, et al. (1992) Live enteroviral vaccines for the emergency nonspecific prevention of mass respiratory diseases during fall-winter epidemics of influenza and acute respiratory diseases. Zh Mikrobiol Epidemiol Immunobiol (11-12): 37-40.

20. Zhang AJ, Lee ACY, Woo Chan JF, Liu F, Li C, et al. (2021) Coinfection by severe acute respiratory syndrome coronavirus 2 and influenza A(H1N1)pdm09 virus enhances the severity of pneumonia in golden Syrian hamsters. Clin Infect Dis 72(12): e978-e992.

21. Laurie KL, Horman W, Carolan LA, Chan KF, Layton D, et al. (2018) Evidence for viral interference and crossreactive protective immunity between influenza B virus lineages. J Infect Dis 217(4): 548-559.

22. Chan KF, Carolan LA, Korenkov D, Druce J, McCaw J, et al. (2018) Investigating viral interference between influenza A virus and human respiratory syncytial virus in a ferret model of infection. J Infect Dis 218(3): 406-417.

23. Schneider WM, Chevillotte MD, Rice CM (2014) Interferonstimulatedgenes: a complex web of host defenses. Annu Rev Immunol 32: 513-545.

24. Huang IC, Li W, Sui J, Marasco W, Choe H, et al. (2008) Influenza A virus neuraminidase limits viral superinfection. J Virol 82(10): 4834-4843.

25. Shinjoh M, Omoe K, Saito N, Matsuo N, Nerome K (2000) In vitro growth profiles of respiratory syncytial virus in the presence of influenza virus. Acta Virol 44(2): 91-97.

26. Goto H, Ihira H, Morishita K, Tsuchiya M, Ohta K, et al. (2016) Enhanced growth of influenza A virus by coinfection with human parainfluenza virus type 2. Med Microbiol Immunol (Berl) 205: 209-218.

27. Nickbakhsh S, Mair C, Matthews L, Reeve R, Johnson PCD, et al. (2019) Virus-virus interactions impact the population dynamics of influenza and the common cold. Proc Natl Acad Sci 116(52): 27142-27150.

28. Rott R, Klenk HD, Nagai Y, Tashiro M (1995) Influenza viruses, cell enzymes and pathogenicity. Am J Respir Crit Care Med 152(4 Pt 2): S16-S19.

29. Tashiro M, Ciborowski P, Klenk H, Pulverer G, Rott R (1987) Role of staphylococcus protease in the development of influenza pneumonia. Nature 325(6104): 536-537.

30. Tashiro M, Ciborowski P, Reinacher M, Pulverer G, Klenk HD, et al. (1987) Synergistic role of staphylococcal proteases in the induction of influenza virus pathogenicity. Virology 157(2): 421-430.

31. Akaike T, Molla A, Ando M, Araki S, Maeda H (1989) Molecular mechanism of complex infection by bacteria and virus analyzed by a model using serratial protease and influenza virus in mice. J Virol 63(5): 2252-2259.

32. Hausler WJ, Sussman M (1998) Topley and Wilson's Microbiology and Microbial Infection. In: 9th (Edn.), Bacterial Infections. Arnold, London, United Kingdom.

33. Reynolds HY, Root EK (1991) Bronchiectasis and broncholithiasis. In: Wilson JD, Braunwald E, et al (Eds.), Harrison's Principles of Internal Medicine. McGraw-Hill, New York, USA, pp: 1069-1071.

34. Tristam DA, Hicks W, Hard R (1998) Respiratory syncytial virus and human bronchial epithelium. Arch Otolaryngol Head Neck Surg 124(7): 777-783.

35. Walsh J, Dietlein LF, Low FN, Burch GE, Mogabgab WJ (1960) Bronchotracheal response in human influenza. Type A, Asian strain, as studied by light and electron microscopic examination of bronchoscopic biopsies. Arch Intern Med 108: 376-388.

36. Hirano T, Kurono Y, Ichimiya I, Suzuki M, Mogi G (1999) Effects of influenza A virus on lectin-binding patterns in murine nasopharyngeal mucosa and on bacterial colonization. Otolaryngol Head Neck Surg 121(5): 616-621.

37. Sanford BA, Shelokov A, Ramsay MA (1978) Bacterial adherence to virus infected cells: a cell culture model of bacteria super-infection. J Infect Dis 137(2): 176-181.

38. Austin RM, Daniels CA (1978) The role of protein A in attachment of staphylococci to influenza-infected cells. Lab Investig 39(2): 128-132.

39. Larson HE, Parry RP, Gilchrist C, Luquetti A, Tyrrell DA (1977) Influenza viruses and staphylococci in vitro: some interactions with polymorphonuclear and epithelial cells. Br J Exp Pathol 58(3): 281-292.

40. Warr GA, Jakab GJ, Chan TW, Tsan MF (1979) Effects of viral pneumonia on lung macrophage lysosomal enzymes. Infection and Immunity 24(2): 577-579.

41. Warr GA, Jakab GJ, Chan TW, Tsan MF (1979) Effects of viral pneumonia on lung macrophage lysosomal enzymes. Infect Immun 24(2): 577-579.

42. Pang G, Clancy R, Gong M, Ortega M, Ren ZG, Reeves G (2000) Influenza virus inhibits lysozyme secretion by sputum neutrophils in subjects with chronic bronchial sepsis. Am J Respir Crit Care Med 161(3): 718-22.

43. Kilbourne ED (1987) Influenza. Plenum Publishing Corp, New York, USA.

44. Schwarzmann SW, Adler JL, Sullivan RJ, Marine WM (1971) Bacterial pneumonia during the Hong Kong influenza epidemic of 1968–69. Experience in a city-county hospital. Arch Intern Med 127(6): 1037-1041.

45. Taubenberger JK, Reid AH, Fanning TG (2000) The 1918 influenza virus: a killer comes into view. Virology 274(2): 241-245.

46. Cartwright KAV, Jones DM, Smith AJ, Stuart JM, Kaesmarski EB, et al. (1991) Influenza A and meningococcal disease. Lancet 338(8766): 554-557.

47. Kim PE, Musher DM, Glezen WP, Rodriguez Barradas MC, Nahm WK, et al. (1996) Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution and isolation of respiratory viruses. Clin Infect Dis 22(1): 100-106.

48. Fiore AE, Iverson C, Messmer T, Erdman D, Lett SM, et al. (1998) Outbreak of pneumonia in a long term care facility: antecedent human parainfluenza virus 1 infection may predispose to bacterial pneumonia. J Am Geriatr Soc 46(9): 1112-1117.

49. Heiskanen Kosma T, Korppi M, Jokinen C, Kurki S, Heiskanen L, et al. (1998) Etiology of childhood pneumonia: serologic results of a prospective, population based study. Pediatr Infect Dis J 17(11): 986-991.

50. Makela MJ, Puhakka T, Ruuskanen O, Leinonen M, Saikku P, et al. (1998) Viruses and bacteria in the etiology of the common cold. J. Clin. Microbiol 36(2): 539-542.

51. Klenk HD, Rott R, Orlich M (1977) Further studies on the activation of influenza virus by proteolytic cleavage of the haemagglutinin. J Gen Virol 36(1): 151-161.

52. Scheiblauer H, Reinacher M, Toshiro M, Rott R (1992) Interaction between bacteria and influenza A virus in the development of influenza pneumonia. J Infect Dis 166(4): 783-791.

53. Tashiro M, Ciborowski P, Klenk HD, Pulverer G, Rott R (1987) Role of staphylococcus protease in the development of influenza pneumonia. Nature 325(6104): 536-537.

54. Tashiro M, Ciborowski P, Reinacher M, Pulverer G, Klenk HD, et al. (1987) Synergistic role of staphylococcal proteases in the induction of influenza virus pathogenicity. Virology 157(2): 421-430.

55. Steczny K, Kokoszynski D (2021) Effects of probiotic preparations (EM) on productive characteristics, carcass composition and microbial contamination in a commercial broiler chicken farm. Anim Biotechnol 32(6): 758-765.

56. Gadde U, Kim WH, Oh ST, Lillehoj HS (2017) Alternatives to antibiotics for maximizinggrowth performance and feed efficiency in poultry A review. Anim Health Res Rev 18(1): 26-45.

57. Salzman NH, Ghosh D, Huttner MK, Paterson Y, Bevins CL (2003) Protection agains enteric salmonellosis in transgenic mice expressing a human intestinal defensin. Nature 422(6931): 522-526.

58. Raghuwanshi S, Misra S, Sharma R, Ps B (2018) Probiotics nutritional therapeutic tool. Journal of Probiotics & Health 6(1): 1000194.

59. Salminen S, Collado MC, Endo A, Hill C, Lebeer S, et al. (2021) The International Scientific Assotiation of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. Nature Reviews Gastroenterology & Hepatology 18(9): 671-671.

60. Abd El Hack ME, El Saadony MT, Shafi ME, Qattan SYA, Batiha GE, et al. (2020) Probiotics in poultry feed: A comprehensive review. J Anim Physiol Anim Nutr (Berl) 104(6): 1835-1850.

61. Arif M, Akteruzzaman M, Ferdous TA, Islam SS, Da BC, et al. (2021) Dietary suplementation of Bacillus-based probiotics on the grouth performance, gut morphology, intestinal microbiota and immune response in low biosecurity broiler chickens. Vet Anim Sci 14: 100216.

62. Manafi M, Khalaji S, Hedayati M, Pirany N (2017) Efficacy of Bacillus subtilis and bacitracin methylene disalicylate on grouth performance, disgestibility, blood metabolites, immunity and intestinal microbiota after intramuscular inoculation with Escherihia coli in broilers. Poult Sci 96(5): 1174-1183.

63. Sikandar A, Zaneb H, Nasir A, Rehman A, Kashif M, et al. (2022) Effect of Bacillus subtilis on the microarchitectural development of the immune system in Salmonella-challenged broiler chickens. Vet Med 67(1): 28-37.

64. Maugg D (2023) How the microbiome influences the success of cancer therapy.