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Otolaryngology Open Access Journal
ISSN: 2476-2490

Some Opportunities that the Covid-19 Pandemic has Shown us

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Mini Review

Volume 9 Issue 1

Received Date: January 18, 2024

Published Date: March 11, 2024

DOI: 10.23880/ooaj-16000288

Abstract

Emerging or re-emerging viral infections significantly affect human health. In recent decades, we have observed the emergence of new diseases in different geographical areas caused by a large number of highly pathogenic viruses belonging to the families Filoviridae, Arenaviridae, Bunyaviridae, Paramyxoviridae, Coronaviridae, Flaviviridae, Togaviridae and Hepeviridae. All of them have a zoonotic origin. Climatic and environmental changes, population mobility, uneven population density, unequal sanitary conditions, change in animal habitats and anthropophilic vectors have led to increased pressure on the host-pathogen-environment system. The more we impact on the nature, the more likely we are to disrupt ecosystems and create conditions for diseases to develop and spread.

Conclusion: The possibility suggested by the last pandemic is that only linking the One health approach to the infectious spectrum, dietary interventions, factors determining human susceptibility to infections, vaccinations-universal, unrelated and local, testing platforms for potential pathogens, pre- and probiotics will help us better deal with such challenges. All of them can help us in developing effective control and protection measures against viral pathogens. Differences in emerging and re-emerging infections must be considered. Knowing and properly using the negative interactions between viral and bacterial pathogens and the human microbiota and inhibiting their positive interactions will help us in combining pharmacological, non-pharmacological and dietary interventions in the personalized treatment of patients with diseases caused by viral pathogens.

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

Abbreviations: DC: Dentritic cells; DC-SIGN: Dentritic Cell-Specific Intercellular Adhesion Molecule-3-Grabing Non-Integrin; HA: Hemagglutinin Esterase; HMPV: Human Metapneumovirus; HRV: Human Rhino Virus; IAV: Influenza A 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; NAAT: Nucleic Acid Amplification Test; OS: Overall Survival; PFS: Progression Free Survival; RSV: Respiratory Syncytial Virus; SARSCoV: Severe Acute Respiratory Syndrome Coronavirus; SLAP: Lactobacillus Surface Layer Protein.

Introduction

Emerging or re-emerging viral infections significantly affect human health. Climatic and environmental changes, population mobility, uneven population density, unequal sanitary conditions, change in animal habitats and anthropophilic vectors have led to increased pressure on

the host-pathogen-environment system. With the expansion of equatorial climatic zones to the present subtropical and temperate climatic zones, pathogens, infectious diseases and their vectors appear in new territories where we have not previously encountered the diseases they cause. Currently, about 55% of the world's population lives in cities. Half a century ago, this indicator was only 35%. The more we impact on the nature, the more likely we are to disrupt ecosystems and create conditions for diseases to develop. Big cities provide a new home for wild animals and birds. They inhabit green spaces and feed on the waste we generate. Wild species often adapt better in cities than in the wild, because they find an abundance of food. This creates excellent conditions for the evolution of diseases. New infections are capable of spreading rapidly in large cities. There, people gather in large numbers in one place, breathe the same air, touch the same surfaces [1,2].

In recent decades, we have observed the emergence of new diseases in different geographical areas caused by a large number of highly pathogenic viruses belonging to the families Filoviridae, Arenaviridae, Bunyaviridae, Paramyxoviridae, Coronaviridae, Flaviviridae, Togaviridae and Hepeviridae. All of them have a zoonotic origin. The COVID-19 pandemic has caused about 699 million cases and resulted in about 6.958 million deaths worldwide. (12.2023) Coronaviruses belong to the group of respiratory viruses [3] Prior to the global COVID-19 pandemic in 2020, coronavirus diseases were primarily of veterinary interest. Even before that, mankind faced 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 [4-7]. They are all caused by RNA viruses. Only the second plague pandemic (1346-1350) caused by Yersinia pestis was more deadly-killing 30-50% of the population of Afro-Eurasia. [8,9] The aforementioned pandemics provoke us to conduct in-depth research on viral pathogens causing emerging and/ or re-emerging infections in the human population.

Zoonoses or diseases of animal origin are diseases transmitted from animals to humans [10]. They pose a great threat to human health and life, as animals are often asymptomatic carriers of pathogens and spread them in the environment with their excreta. Among recognized pathogens causing human disease, about 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. Of the 1,400 pathogens that cause disease in humans, 800 are of animal origin [11,12]. The key to unraveling the emergence and/ or re-emergence of viral pathogens is the host-pathogen-environment relationship. Modes of transmission include direct contact, abrasions and skin injuries, bites, through food, soil and water, and sometimes the same infection can be transmitted in several ways.Vectors for their transmission include ticks, fleas, mosquitoes, arthropods and rodents. Shepherds, farmers, zookeepers, hunters, slaughterhouse workers and veterinarians are among the most commonly affected occupations [1,13].

Viral pathogens include DNA and RNA viruses. DNA viruses are thought to have evolved over millions of years [3,14]. RNA viruses have adapted to the human population for about 1000 years. From DNA viruses, 87% have adapted to humans, while only a small part of RNA viruses have [15]. The adaptation has occurred through mutations, rearrangements or gene recombinations, leading to the formation of stable viral lineages in the human population. Some of them may circulate asymptomatically, until their new clinical manifestations are detected [16]. The origin of most human viruses is unknown, but most can be categorized as "crowd diseases", requiring relatively high population densities to stabilize [1,17]. 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, with man is often just an "accidental" host. Only a small part of these viruses are able to persist in certain human populations (endemics) or spread between different populations (epidemics) [18].

The types of macroorganisms in which a given microbial species can cause infection is referred to as the infectious spectrum of the respective species. It is of primary importance for any emerging or re-emerging viral infection to determine the infectious spectrum. In some microorganisms it is very wide. For example, rabies virus causes infections in all mammals, while mumps virus causes infection and disease only in humans or has a narrow infectious spectrum.

The development of effective measures for control and protection against viral pathogens is a serious challenge. It will enable us to properly combine pharmacological, non-pharmacological and dietary interventions and control the risk of developing such diseases. These measures will be half-hearted if interactions between both circulating viral and bacterial pathogens and the human microbiota and genome are not studied and understood. It is important to determine the type of these interactions - synergistic or antagonistic, their nature - short-term or long-term, and how the interaction can change the individual's susceptibility to infection and the severity of the course.

The human microbiota consists of commensal, symbiotic and pathogenic microorganisms, and their interaction is the basis of our health and immunity. The interaction/competition between commensal and potentially pathogenic bacterial species in the nose and nasopharynx is involved in the regulation of pathogenic species and host responses. This is due to the production of antimicrobial peptides (bacteriocins), which directly inhibit the growth or survival of the pathogen. The human microbiota is estimated at 39 to 44 billion microbes or about ten times more than the number of cells in the human body. It performs a barrier function on the epidermis, mucous membranes, gastrointestinal tract, lungs and urogenital system. The microbiome is estimated to have 8 million genes compared to 20 – 25,000 human genes. At the heart of the pathogenesis of upper and lower respiratory tract infections is the interaction between respiratory viruses, bacteria, microbiota and the host's innate immune responses. From the respiratory viruses, those that most often attack the human respiratory tract are: influenza virus, parainfluenza virus, RSV, adenoviruses, measles virus, rhinoviruses and coronaviruses [3].

Bacterial pathogens that are most often found in the respiratory tract are: Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae, Staphylococcus aureus, Neisseria meningitidis, Mycobacterium tuberculosis, Bordetella pertussis and in immunocompromised patients Pseudomonas aeruginosa [19]. The nasal and nasopharyngeal microbiota consist of various types of aerobic and anaerobic microorganisms. Their composition is not constant throughout our life and begins to form immediately after our birth. It is directly dependent on the environment, the season, socio-economic living conditions, nutrition, vaccinations, past illnesses, harmful habits, taking antibiotics and etc. The barrier function plays an important role in protecting us from infections. In a healthy microbiota or eubiosis, commensal bacteria suppress the colonization of opportunistic pathogens. An example of this is the bacteriocins of Streptococcus salivarius, which inhibit Streptococcus pneumoniae, and the bacteriocins of *E. coli* strains, which inhibit intestinal enterohemorrhagic *E. coli* [20-22]. Another observed variant of inhibition is the colonization of a comparable species with which the pathogen shares antigens. This is seen with Neisseria lactamica and Neisseria meningitidis. Proteins on the membrane and lipooligosaccharide structures are the antigenic sources for cross-protection [23]. In turn, bacterial pathogens can have an immunizing effect, stimulating both our humoral and cellular immune responses [24,25].

The occurrence of dysbiosis of the nasal and nasopharyngeal microbiota leads to pathogenic overgrowth, greater susceptibility to infection, and the possibility of dissemination to the lower respiratory tract and gastrointestinal tract. The upper respiratory tract is a natural habitat for a large number of commensal bacteria. These include a number of potentially pathogenic bacteria that colonize these areas without progression to disease, but when they spread to the lungs or blood, can cause very serious infections such as meningitis, pneumonia, and septicemia. The relationship between the bacteria colonizing the nose and nasopharynx is delicately balanced and any disturbance leads to the possibility of pathogenic microorganisms causing disease. Factors that can disturb this fine balance are: colonization by new species, viral and bacterial interactions, host-pathogen interaction, prior antibiotic therapy and environmental changes. Studies in animal models demonstrate how bacterial species compete with each other for colonization. This occurs in two ways: passive inhibition by occupying the same ecological place and active by directly inhibiting the growth or killing of competing species. Nasopharyngeal colonization with Streptococcus pneumoniae protects us from Staphylococcus aureus and reduction of the microbial count of *S. pneumoniae* after pharmacological intervention leads to increased carriage of S. aureus [26,27]. Lack of microbial colonization in mice enhances allergic airway inflammation and colonization with a high number of species protects against inflammation [28-30]. The very good is not good principle can be seen in the eradication of all 93 strains of Streptococcus pneumoniae from the nasopharynx. In this case, the elimination of competition from *S. pneumoniae* against other potential pathogens may cause their overgrowth, leading to an increased incidence of diseases caused by H. influenzae, S. aureus, N. meningitidis and M. Catarrhalis [31,32].

Potential viral interactions are important in the context of elucidating their possible cooperation with some of the bacterial pathogens of the microbiome. They will allow us to predict which respiratory diseases may be more severe and this would help us to better adapt the therapeutic approach in these patients.The interactions are of three types: a) the virus potentiates bacterial colonization, b) the proteases of the respiratory tract bacteria induce structural changes leading to increased pathogenicity and tissue tropism of the virus and c) the bacteria enhance viral infection by activating host proteases [33-36]. The cooperation of 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 [37-41].

Bacterial colonization of airway surfaces is facilitated when mucociliary clearance is impaired by a previous viral attack, but bacterial lung infection is more common in primary ciliary dyskinesia [42]. RSV has been found to cause loss of cilia in human bronchial cells in vitro and influenza virus has been found to cause damage to the ciliated epithelium and

bronchial epithelial lining [43,44]. A virus-induced change in the membrane potential of host cells is considered the most likely reason for the increased bacterial adhesion. Viral glycoproteins expressed on host cell membranes can serve as receptors for bacteria. A study shows that hemagglutinin esterase (HA) of influenza virus on infected MDCK cells acts as a receptor for group B streptococci. In more recent studies, the change in glucoconjugate structure of murine nasopharyngeal mucosa caused by influenza infection is associated with changes in lectin binding patterns [45,46]. 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 in influenza infection virus aids tissue penetration. 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 [47,48]. Viral infection can suppress the host's defense mechanisms against bacterial attack-nonspecific humoral factors, nonspecific phagocytosis by neutrophils and macrophages at the beginning of the infection and a later immune response mediated by specific antibody. Influenza virus-induced polymorphonuclear dysfunction is an important condition for influenza virus-potentiated secondary pneumococcal diseases. After interaction with it in human neutrophils in vitro, reduced chemotaxis and phagocytic activity were observed when interacting with staphylococci [49]. The mechanism of reduction of the bactericidal power of neutrophils and macrophages after influenza virus infection is expressed in the disruption of lysozyme production by both types of phagocytes [50,51]. 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. Much work remains to elucidate the interaction of influenza viruses with commensal bacteria colonizing the lower respiratory tract and their likely relation to fatal complications. Influenza, pneumococcal infection and meningococcal disease have a seasonal relationship - they occur in the winter months [2,52-56]. Similar interactions with Streptococcus pneumoniae are found in RSV and human parainfluenza virus [52,55,56]. Unlike most respiratory viruses, human rhinoviruses and seasonal coronaviruses (HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1) appear to act independently [57]. Elucidation in SARS-CoV-2 of possible positive cooperation with bacterial pathogens is pending.

Proteases of respiratory tract bacteria can induce the cleavage of influenza virus HA and increase the pathogenicity of the virus in vivo. These are supposed to be staphylokinase, streptokinase and others by generating plasmin from plasminogen. This was first established for the protease of Staphylococcus aureus and then for those of Streptomyces griseus and Aerococcus viridans. Cleavage of HA from S. aureus and A. viridans not only confers virus infectiousness and replication capacity in vitro, but also increases virus replication and pathogenicity in mice [34-36,58-60].

During the same annual period, several respiratory viruses may circulate simultaneously. Cocirculation of viral pathogens can lead to multiepidemics, such as the combination of COVID-19, RSV and influenza or a recent viral infection can induce a refractory period during which the host is unlikely to be infected by another respiratory virus. To understand their interactions, it is of paramount importance to determine whether the viruses share the same environmental conditions (seasonality) – 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 virus-induced innate immune response pattern in the upper and lower respiratory tract [61].

Viruses 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 weaken 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 [62]. The negative virus-virus interaction is homologous and heterologous depending on whether the 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 (influenza virus A - IAV and RSV) [63-65]. 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 is found primarily in epithelial cells of the gastrointestinal and respiratory tract Secreted IFNs bind to receptors on the surface of infected and neighboring cells. Viral defense is expressed in the production of effectors that directly inhibit

viral replication, as well as chemokines and cytokines [66-68]. In the 1960s, Voroshilova et al. develop the concept of viral interference. They suggest that the likely mechanism is due to the IFN response that provides temporary non-specific immunity to the host [69]. The live enterovirus vaccines (LEV) they developed from attenuated enteroviruses are used to prevent enteric disease due to unrelated enteric pathogens in children. They found that, in addition to a protective effect of LEV against pathogenic enteroviruses, particularly polioviruses, oral administration 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 respiratory viruses mentioned above. This effect suggests the phenomenon of viral interference [70]. 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 determine 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. Markers for such an 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 by time of coinfection with IAV in MDCK cells by competition for viral protein synthesis [71,72]. 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 proinflammatory cytokines or by reduced secretion of non-inflammatory mediators such as interleukin (IL) 10 [73]. 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. 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.

Modern viral molecular testing platforms are highly accurate, but not infallible. At low virus circulation, the deficiencies in their specificity and sensitivity increase. The negative predictive value is higher than the false positive rate of testing. Samples taken from the nasopharynx according to various studies have a sensitivity of 88 to 95%. Developed laboratory platforms can test for dozens of potential pathogens, including bacteria. Rapid NAATs have the ability to isolate SARS-CoV-2, influenza and RSV. These infections are usually difficult to distinguish based on clinical manifestations alone. Viral coinfection triggers respiratory bacterial infections in the nasopharynx, causing dysbiosis. An individual's susceptibility to infection is usually associated with high levels of polymicrobial colonization. Our results allow for easier treatment decision-making, as well as management of infection control measures in patients with acute upper respiratory tract diseases.

Factors determining a person's susceptibility to infection are: age, sex, health status, diet, exposure to the pathogen, co-infection, current state of immunity and the individual's genome. Using the results obtained from the research conducted, our knowledge of the interactions of viral and bacterial pathogens and the microbiota, and the factors that determine human susceptibility to infection will allow us to more correctly combine pharmacological, non-pharmacological and dietary interventions and better treat such diseases.

Using diet and dietary interventions can give us some advantages in dealing with infections. Probiotics are defined by Fuller as live organisms contained in food that, when ingested, can alter the gut microbiota and stimulate the immune system after ingestion. These live microorganisms, taken in sufficient quantity, have a certain benefit for the health of humans and animals. Separately, they have proven to be an alternative to antibiotics in poultry farming [74]. They can be a single strain or a combination of strains, and their main properties include – acid resistance, strain specificity, lack of side effects, reduction of pathogenic microbial numbers and storage viability. Following oral administration of a mixture of Lactobacillus rhamnosus GG, Bifidobacterium, Lactobacillus acidophilus and Streptococcus thermophilus, as well as Lactobacillus plantarum alone, a limitation of nasal colonization with potential pathogens and a reduction in the frequency of upper respiratory tract infections were observed. These microorganisms in the gut can enhance local mucosal immunity by interacting with the gut immune system [75]. The benefit of probiotics for overall health is expressed in competitive inhibition (competing with pathogenic bacteria for access to nutrients and limiting their colonization in the intestine), production of antibacterial substances and organic acids, antagonism with viral pathogens against their entry and replication , immunomodulating properties (improving humoral immunity), improving the absorption of proteins and minerals, detoxifying metabolites toxic to the kidneys and regulating the homeostasis of the intestinal microbiota [76-80] The intestinal microbiota is the largest and the dysbiosis is associated with various pathologies, including cancer. It locally and systemically influences the immunomodulating functions - reduction of inflammation, antitumorogenesis and suppression of tumor growth, and improvement of the intestinal barrier. In dysbiosis and carcinogenesis,

protective immunomodulatory functions are switched off, which promotes inflammation and uncontrolled tumor growth. Probiotics affect the composition and activity of the intestinal microbiota and limit colonization with pathogenic microorganisms. Possible mechanisms include reduction of gastrointestinal pH, modulation of the immune system and production of organic acids. Separately, the improvement the integrity of the intestinal barrier, the breakdown of food, synthesis in vitamins, enhanced immunogenicity and correction of microbial signaling pathways in the cells of the intestinal epithelium were observed [81].

The genus Lactobacillus is a common inhabitant of the gastrointestinal tract of humans and animals [82].

The ability of Lactobacillus to adhere to epithelial surfaces is critical for maintaining persistent colonization in the mammalian gut and other tissues. Many species of the genus Lactobacillus possess a surface layer protein (SLAP) that forms the outermost envelope of the cell. Lactobacillus acidophilus is well studied. It is one of the strains of the genus Lactobacillus found in the human gut and due to their probiotic characteristics are recognized as safe. In the gastrointestinal tract (GIT), L. acidophilus regularly encounters many antigen presenting cells, dendritic cells (DC) [83]. These cells express DC specific ICAM-3 capture protein (DC-SIGN), which is a cell surface receptor and which is mainly presented on DC. It recognizes the mannose- and fructoseglycans that are present on the surfaces of microbes and viruses.

DCs play a very important role in the innate and adaptive immune response [84]. It has been shown that DC-SIGN can enhance cellular entry of various viruses such as HIV type 1, hepatitis C, Ebola, Dengue, and SARS [59]. DCs have also been shown to interact with L. acidophilus. This contact involves DC-SIGN and the S surface protein layer presented on the bacterial cell envelope and regulates the induction of a number of cytokines involved in cellular immune regulation [85,86]. Li et al. found that Lactobacillus acidophilus S-layer protein inhibited bacteria-induced apoptosis. Another member is Lactobacillus delbrueckii subsp. bulgaricus, which through its surface enzymes (cell surface proteinase PrtB) mediates adhesion of Lactobacillus to mucin and human epithelial cells [87]. Lactobacillus bulgaricus is one of the lactic acid bacteria used in industrial milk fermentation. Bulgarian kiselo mljako not yogurt, thanks to Lactobacillus bulgaricus is a natural probiotic that has a strong beneficial effect on humans. One of the first probiotics in the world was developed by Prof. Nikola Alexandrov in the 80s of the 20th century in Bulgaria based on Lactobacillus bulgaricus. Kiselo mljako is a widespread food among the Bulgarian population. A study shows that the nasal microbiota in dairy farmers is more complex and protects against infection and competes with Staphylococcus aureus colonization [88].

Qiu, et al. 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 performed in mouse models have demonstrated disruption of the microbial system of the gastrointestinal tract (change in total number and diversity) 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 inhibitor (ICI) 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 [89]. Numerous studies have demonstrated that it is possible to manipulate the microbiome by increasing the number of immunopotentiating bacteria while at the same time limiting the effectiveness of bacteria with increased immune suppression. Modeling the microbiome through diet, pre- and probiotics suggests the possibility of improving responses in immunotherapy, but also in viral and bacterial infection [90].

Conclusion

The coronavirus pandemic has shown us that only linking the one health approach to the infectious spectrum, the factors that determine human susceptibility to infections, vaccinations-universal, unrelated and local, testing platforms for potential pathogens, the use of dietary interventions, pre- and probiotics will give us facilitate dealing with new epidemics/pandemics.

The adoption of the one health approach to public health will play a huge role in the future. The relationship between human health and must be taken into account, something that was suggested to us during the last pandemic. The human population is only a small, though important part of the Earth's ecosystem. But the approach itself is only part of the problem. Even healthy animals, poultry and the animal products that we consume, can have an impact on public health. The plant protection products used indirectly through their consumption by animals and the antibiotics used in the production of milk, poultry and animal meat can contribute both to the formation of microbial resistance and to the disruption of the microbial population of the gastrointestinal tract (the total number and diversity) in humans. Lactic acid bacteria are widely used in industrial milk fermentation. The above-mentioned factors can lead to a change in the microbial number of these bacteria in milk and milk products, leading to a decrease in their protective effect.

Determining the infectious spectrum of viral pathogens will facilitate the prediction of possible species barrier crossings.

Factors determining a person's susceptibility to infection are extremely important in determining risk. These are age, sex, health status, diet, exposure to the pathogen, co-infection, current state of immunity and the individual's genome. Various studies have shown that microbial diversity increases with age and comorbidity is associated with a more severe course and more frequent complications.

Universal immunization is the first line of defense, which is extremely important if a vaccine is available. It uses vaccines with the same composition, the same doses and the same number of doses in the entire population, provided there are no contraindications. It assumes that each person has the same type of immune response, achieves comparable levels of immunity (whether humoral or cell-mediated) and that everyone requires the same level of antigens to develop immunity. Universal immunization also implies the same level of risk for all people. The weakness is that individual differences in disease risk, immune response, adverse reactions and dosage, nonresponder rate and interval between doses are not taken into account. After vaccination, women are known to respond with higher levels of antibodies than men.

Ethnicity also plays a role due to genetic polymorphism. Also, genetic factors can block the immune response to the vaccine antigen due to the simultaneous administration of a drug preventing the transcription of an immune response gene. Obstacles to the development of personalized vaccines are currently a lack of knowledge about the individual immune response, the genetic variability of pathogens, the host microbiome, environmental factors and other issues. Nevertheless, many infectious diseases have been brought under control as a result of vaccination. Modulation of the immune response by using the Bacillus Calmette-Guérin (BCG) vaccine, influenza, and others to prevent disease from unrelated viral pathogens should also be considered [91-93]. Through developed laboratory platforms, samples taken from the nasopharynx can be tested for dozens of potential pathogens, including bacteria. Potential viral interactions will allow us to predict which respiratory diseases may be more severe, and this would help us better adapt the therapeutic approach in these patients. The most important thing we have yet to clarify is whether these interactions are situationally or genetically determined.

The use of preparations such as local vaccines containing group a streptococci (Streptococcus sanguis, Streptococcus mitis, Streptococcus salivarius and Streptococcus oralis) and agents (carrageenans) early in the disease may help us to disrupt the possibility of synergistic interactions between viral and bacterial pathogens and reduce disease severity. The presumption of this approach lies in the ability to inhibit pathogenic bacteria from the representatives of this group. For example, all representatives inhibit Haemophilus influenzae, Streptococcus oralis inhibits Streptococcus pneumoniae and Streptococcus sanguis inhibits Streptococcus pyogenes. The antiviral effect of carrageenans is most likely based on reduced attachment and entry of the virus into target cells, which reduces the viral load in the nose and nasopharynx and supports the protective function of the microbiota [94,95]. The barrier function of the microbiota plays an important role in protecting us from infections. Factors that can disrupt the eubiosis of the human organism include colonization by new species, viral and bacterial interactions, host-pathogen interactions, prior antibiotic therapy, and environmental changes.

Based on the seasonal circulation of pathogenic viruses and bacteria, we can apply dietary interventions and probiotics to risk groups (children up to 1 year, adults over 65, immunocompromised and patients with accompanying diseases) at the beginning of the season. The use of their capabilities - competitive inhibition, production of antibacterial substances and organic acids, antagonism with viral pathogens against their entry and replication, immunomodulatory properties, improving the absorption of proteins and minerals, detoxification for metabolites toxic to the kidneys and regulating the homeostasis of the intestinal microbiota can offer us serious benefits for human health. In the case of previous treatment of patients from the risk groups with antibiotics, the intake of prebiotics is more expedient, especially during the first forty days, since during digestion prebiotics support the recovery and growth of certain microbiota. Blocking and/or reducing cell surface receptors and competition for cellular resources are seen as negative feedback mechanisms that we must utilize to the maximum.

Each of the above components, alone or in combination, will help us develop effective control and protection measures against viral pathogens. Knowledge and proper use of negative interactions between viral and bacterial pathogens and human microbiota and inhibition of their positive interactions will help us in combining pharmacological, non-pharmacological and dietary interventions in personalized treatment of patients with diseases caused by viral pathogenss. This will also allow us to better control the risk of such diseases occurring.

References

1. Parvez MK, Parveen S (2017) Evolution and emergence of patogenic viruses: Past, present and future, Intervirology

60(1-2): 1-7.

2. (2022) Weekly epidemiological update on COVID-19–31.

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

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

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. Bos KI, Schuenemann VJ, Golding GB, Burbano HA, Waglechner N, et al. (2011) A draft genome of Yersinia pestis from victims of the Black Death. Nature 478(7370): 506-510.

9. Benedictow OJ (2004) The Black Death, 1346-1353: The Complete History. Boydell Press, Martlesham, United Kingdom.

10. European Food Safety Authority (EFSA European Centre for Disease Prevention and Control (ECDC) (2016) The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2015. EFSA J 14(12): e04634.

11. 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.

12. Levin, S. Zoonoses. In Goldman's Cecil Medicine, 24th ed.; Goldman, L., Schafer, A.I., Eds.; W.B., Sounders: Philadelphia, PA, USA, 2012; Chapter 336; pp. 1964–1967, ISBN 9781455753369, 9780323295253, 9781437736083.

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

14. Simmonds P (2011) Reconstructing the origins of human hepatitis viruses. Philos Trans R Soc Lond B Biol Sci 356(1411): 1013-1026.

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

16. 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.

17. Wong A, Guevara LAB, 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.

18. 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.

19. Hausler WJ, M. Sussman (ed.). 1998. Topley and Wilson's Microbiology and Microbial Infection, 9th ed., vol. 3. Bacterial Infections. Arnold, London, United Kingdom.

20. Wescombe PA, Heng NCK, Burton JP, Chilcott CN, Tagg JR (2009) Streptococcal bactericins and the case for Streptococcus salivarius as a model oral probiotics. Future Microbiol 4(7): 819-835.

21. Santagati M, Scillato M, Patane F, Aiello C, Stefani S (2012) Bactericin-producing oral streptococci and inhibition of respiratory pathogens. FEMS Immunol Med Microbiol 65(1): 23-31.

22. Hammmi R, Fernandez B, Lacroix C, Fliss I (2013) Anti-infective properties of bactericins: an update. Cell Mol Life Sci 70(16): 2947-2967.

23. Evans CM, Pratt CB, Matheson M, Vaughan TE, Findlow J, et al. (2011) Nasopharyngeal colonisation by Neisseria lactamica and inductionof protective immunity agains Neisseria meningitidis. Clin Infect Dis 52(1): 70-77.

24. Esposito S, Prinsipi N (2018) Impact of nasopharyngeal microbiota on the development of respiratory tract diseases. Eur J Clin Microbiol Infect Dis 37: 1-7.

25. Huang YJ (2017) Nasopharyngeal microbiota: gatekeepers or fortunetellers of susceptibility to respiratory tract infections. Am J Resp Crit Care Med 196(12): 1504-1505.

26. Regev-Yochay G, Dagan R, Raz M, Carmeli Y, Shainberg B, et al. (2004) Association between carriage of Streptococcus pneumoniae and Staphylococcus aureus in Children. JAMA 292(6): 716-720.

27. Bogaert D, De Groot R, Hermans PWM (2004) Streptococcus pneumoniae colonisation: the key to pneucoccal disease. Lancet infect Dis 4(3): 144-154.

28. Herbst T, Sichelstiel A, Schar C, Yadava K, Bürki K, et al. (2011) Dysregulation of allergic airway inflammation in the absence of microbial colonization. Am J Respir Crit Care Med 184(2): 198-205.

29. Hagner S, Harb H, Zhao M, Stein K, Holst O, et al. (2013) farm-derived Gram-positive bacterium Staphylococcus sciuri W620 prevents asthma phentype in HDM- and OVA-exposed mice. Allergy 68(3): 322-329.

30. Cahenzli J, Koller Y, Wyss M, Geuking MB, McCoy KD (2013) Instetial microbial diversitybduring early-life colonization shpes long-term IgE levels. Cell Host Microbe 14(5): 559-570.

31. Watson k, Carville K, Bowman J, Jacoby P, Riley TV, et al. (2006) Upper respiratory tract bacterial carriage in Aboriginal and non- Aboriginal children in semi-arid area of Western Australia. Pediatr Infect Dis J 25(9): 782-790.

32. Chan WY, Cohen J, Brown J (2016) The new first-line defense: The potential of nasopharyngeal colonization in vaccine strategies. Vaccine development and therapy 6: 47-57.

33. 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.

34. 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.

35. 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: 421-430.

36. 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: 2252-2259.

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

38. Schwarzmann SW, Adler JL, Sullivan RJ, Marine WM (1971) Bacterial pneumonia during the Hong Kong influenza epidemic of 1968-69. Arch. Intern. Med 127(6): 1037-1041.

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

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

41. 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.

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

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

44. Walsh J, Dietlein L, Low F, Burch G, Mogabgab W (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.

45. 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: 616-621.

46. 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: 176-181.

47. Hausler WJ, Sussman M (1998) Topley and Wilson's Microbiology and Microbial Infection. 9th (Edn.), Bacterial Infections. Arnold, London, United Kingdom 52(3): 237-238.

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

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

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

51. Pang G, Clancy R, Gong M, Ortega M, Ren ZG, et al. (2000) Influenza virus inhibits lysozyme secretion by sputum

neutrophils in subjects with chronic bronchial sepsis. Am. J. Respir. Crit. Care Med 161(3 pt 1): 718-722.

52. Kilbourne ED (1987) Influenza. Plenum Publishing Corp, New York, N.Y.

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

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

55. 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.

56. 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.

57. 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.

58. 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.

59. 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: 783-791.

60. 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.

61. Jocelyne P, Boivin G (2022) Viral Interference between Respiratory Viruses. Emerging Infectious 28(2): 273-281.

62. Zhang AJ, Lee AC, 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. Clinical Infectious Diseases 72(12): e978-e992.

63. 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. The Journal of Infectious Diseases 217(4): 548-559.

64. 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. The Journal of Infectious Diseases 218(3): 406-417.

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

66. 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.

67. 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.

68. 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.

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

70. 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.

71. 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.

72. 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. Medical Microbiology and Immunology 205: 209-218.

73. 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 U S A 116: 27142-27150.

74. Soren S, Mandal GP, Roy B, Samanta I, Hansda RN (2023) Assessment of Bacillus subtilis based probiotics on health and priductive perfomance of poultry: A review. Indian J Anim Health 62(2): 132-138.

75. Gluck U, Gebbers JO (2003) Ingested probiotics reduce nasal colonization with pathogenic bacteria (Staphylococcus aureus, Streptococcus pneumoniae, and beta-hemolytic streptococci). Am J Clin Nutr 77(2): 517-520.

76. 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.

77. 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.

78. 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.

79. Raghuwanshi S, Misra S, Sharma R, Ps B (2018) Probiotics nutritional therapeutic tool. Journal of Probiotics & Health 6(1): 1-8.

80. 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. Nat Rev Gastroenerol Hepatol 18(9): 649-667.

81. Abdel Hack ME, El Saadony MT, Shafi ME, Qattan SYA, Batiha GE, et al. (2019) Probiotics in poultry feed: A comprehensive review. J Anim Physiol Anim Nutr 104(6): 1835-1850.

82. Heng NC, Hammes WP, Loach DM, Tannock GW, Hertel C (2003) Identification of Lactobacillus reuteri genes specifically induced in the mouse gastrointestinal tract. Appl Environ Microbiol 69: 2044-2051.

83. Li P, Yin Y, YU Q, Yang Q (2011) Lactobacillus acidophilus S-layer protein-mediated inhibition of Salmonella-inducing apoptosis in Caco-2 cells. Biochem. Biophys Res Commun 409: 142-147.

84. Penders J, Thijs C, Mommers M, Stobberingh EE, Dompeling E, et al. (2010) Intestinal Lactobacilli and the DC-SIGN gene for their recognition by dendritic cells play a role in the aetiology of allergic manifestations. Microbiology 156(Pt11): 3298-3305.

85. Khoo US, Chan KY, Chan VS, Lin CL (2008) DC-SIGN and L-SIGN the SIGNs for infection. J Mol Med Berl 86(8): 861-874.

86. Alen MM, Kaptein SJ, De Burghgraeve T, Balzarini J, Neyts J, et al. (2009) Antiviral activity of carbohydrate-binding agents and the role of DC-SIGN in dengue virus infection. Virology 387(1): 67-75.

87. Konstantinov SR, Smidt H, de Vos WM, Bruijns SCM, Kaur Singh S, et al. (2008) S layer protein A of Lactobacillus acidophilus NCFM regulates immature dendritic cell and T cell functions. Proc Natl Acad Sci USA 105(49): 19474-19479.

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

89. Hyun Mi K, Jin Han K (2021) Effects of nasopharyngeal microbiota in respiratory infections and allergies. Clin Exp Pediatr 64(11): 543-551.

90. Leveraging the microbiome to strenghten immune therapeutic response. White paper, Perkins Elmer pp: 1-4.

91. Kennedy RB, Ovsyannikova IG, Lambert ND, Haralambieva IH, Poland GA (2014) The Personal Touch: Strategies Toward Personalized Vaccines and Predicting Immune Responses to Them. Expert Rev Vaccines 13(5): 657-669.

92. Poland GA, Ovsyannikova IG, Jacobson RM (2021) Personalized Vaccines: The Emerging Field of Vaccinomics. Expert Opin Biol Ther 8(11): 1659-1667.

93. Kennedy RB, Ovsyannikova IG, Palese P, Poland GA (2020) Current Challenges in Vaccinology. Frontiers in Immunology 11: 1181.

94. McKim JM, Willoughby JA, Blakemore WR, Weiner ML (2019) Clarifying the confusion between poligeenan, degraded carrageenan, and carrageenan: a review of the chemistry, nomenclature, and in vivo toxicology by the oral route. Crit Rev Food Sci Nutr 59(19): 3054-3073.

95. Hebar A, Koller C, Seifert JM (2015) Non-clinical safety evaluation of intranasal iota-carrageenan. PLoS One 10(4): e0122911.