Review article

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EVOLUTION, REVOLUTION, LIFE

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The main aim of this article is to present vaccination as an important factor in the relationship between humans and microorganisms, as well as to emphasize that knowledge about that relationship is significant for generating efficient vaccines. The co-evolution of humans and pathogenic microorganisms is a long-lasting dynamic process. In the course of this relationship some of these microorganisms have had detrimental effects on human populations, while some have adjusted to the host and are now considered beneficial. If we think about the time period of this co-evolution, vaccination has only recently been introduced as a novel factor in the relationship. Not only is it novel, it is also revolutionary in its nature. Thanks to vaccination, numerous diseases caused by pathogenic microorganisms may be eradicated. Vaccination is a powerful man-made selective pressure. This article deals with the co-evolution between microorganisms and humans, with the revolution involved in it, and explains how these reflect on different perspectives of human life. **Conclusion.** Vaccination, as a revolutionary approach in the co-evolution of humans and pathogenic microorganisms, must be designed carefully for each of the pathogens. Thus, a better understanding of our co-evolution with pathogenic microorganisms, at both genetic and physiological levels, is necessary for designing improved vaccination strategies.

Introduction

"Now that I understand this right
Let me take it to the mic
This revolution
Has just begun"
Tricky

Homo sapiens has had a long lasting co-evolution with many bacteria, viruses and other microorganisms. Most of these microorganisms are not harmful to humans, and in many cases they have been proven to be beneficial, as they serve as commensal organisms that have profound roles in various bodily functions, such as digestion, nervous system development, immune response and behavior (1). Actually, the development of the adaptive immune system has been closely related evolutionarily to the symbiotic interaction of vertebrates with gastrointestinal tract microorganisms (Fig. 1) (2, 3). Also, some viruses have incorporated their genetic material into human DNA, and these are now inherent parts of the human genome. Approximately 8% of the human genome is made from human endogenous retrovirus sequences (4). Some of these sequences are necessary for maintaining basic functions in humans, formation of the placenta being the

most striking example (5). For commensal microorganisms, peaceful and mutually useful co-existence is the way for survival and propagation. Still, there are pathogenic microorganisms that use the opposite tactic. They exploit host resources, cause harm to the host, and tend to be transmitted within the host population either vertically or horizontally. In order to propagate their species, pathogenic microorganisms usually do not cause high mortality or disability in human populations, as this would prevent their efficient spread. Of course, it is not only up to microorganisms to decide if the disease they are causing is going to be more or less serious. The immune system has a dominant role in the relationship between pathogenic microorganisms and humans. Thus, it is necessary to know both pathogenic microorganisms and human immune system genetics and functions in order to understand the outcome of the relationship (6).

An attempt will be made in this paper to provide answers to the following questions: 1. Is there a microorganism that could lead to the extinction of humans? 2. Why are there microorganisms that cause high-mortality diseases? 3. Is it possible to have a symbiotic relationship with a pathogenic microbe? 4. Does vaccination shift the balance between pathogenic microorganisms and humans? These answers will contain some explanations

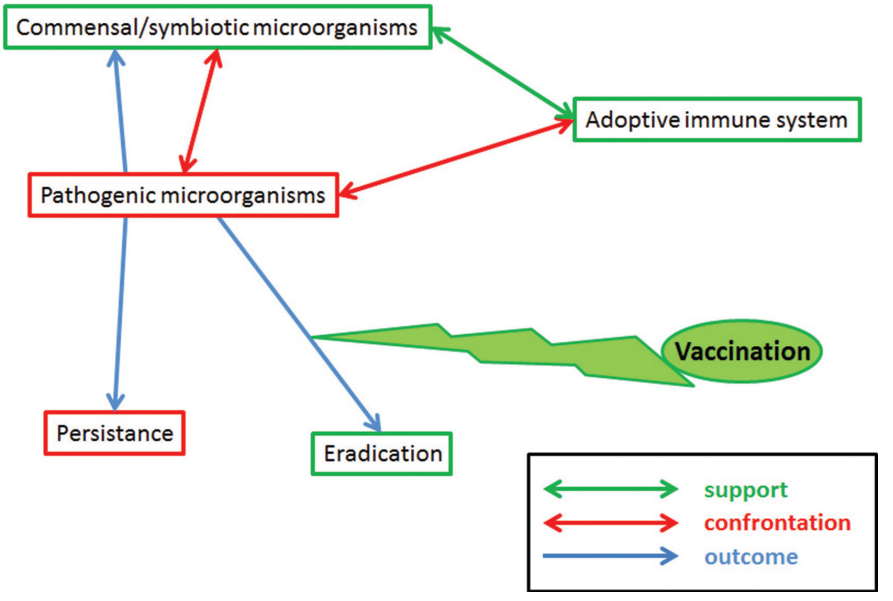

Fig. 1 *Vaccination as a revolution in co-evolution of humans and microorganisms. There are many commensal/symbiotic organisms in human body, including the microbiota of gastrointestinal, respiratory, urogenital tract and skin. These microorganisms contribute to various bodily functions. They are one of the main factors in the development and activity of the adaptive immune system in humans. Adaptive immune system and these microorganisms interact in a such a way to support each other. Pathogenic microorganisms are in conflict with the adaptive immune system, as well as with symbiotic microorganisms. This conflict might be resolved in three principal ways. 1. Pathogenic microorganism resists immunity and persists in human populations. 2. They evolve into commensal, or even symbiotic microorganisms. 3. They are eradicated from human population. Vaccination is a revolutionary factor in co-evolution of pathogenic microorganisms and humans. If efficient vaccine against a certain microorganism is produced and if vaccination is conducted properly, eradication of a disease caused by this microorganism in humans will be certain.*

as to how the evolution and revolution of the relationship between humans and microorganisms may nourish life.

They will also contribute to the main aim of this article, i.e. to present vaccination as an important factor in the relationship between humans and microorganisms, as well as to emphasize that knowledge about that relationship is significant for generating efficient vaccines.

Is there any microorganism that could lead to the extinction of humans?

No microorganism that is a 100% efficient killer of humans has been identified so far. On the top of the killer list is *Rabies lyssavirus*, the virus that causes Rabies. It is widely accepted that Rabies is 100% fatal to humans. Luckily, the disease is preventable and may also be treated with post-exposure vaccines. This virus is neurotropic. It enters neurons and migrates towards the brain. Its migration is rather slow and it takes several weeks for the virus to reach the brain and induce Rabies symptoms. As long as symptoms do not occur, post-exposure vaccine can be applied efficiently in an infected person. Still, there are people that do not receive vaccines and, as a consequence, more than 55,000 people die from Rabies every year (7). However, there are documented cases of survival, the most famous being that of Jeanna Geise in 2004 (8). Also, there are certain Peruvian populations that are rather frequently exposed to bites from vampire bats, well-known Rabies virus carriers. Detailed surveillance of these populations identified non-vaccinated subjects that had antibodies against the Rabies virus that had never developed the disease symptoms (9). This meant that they were infected with the Rabies virus and that they were able to eliminate the virus. Thus, even without vaccination, Rabies is not 100% lethal for humans. If we take into account the highly efficient vaccines (10) available for prophylaxis and post-exposure treatment, it is clear that the Rabies virus is not an extinction threat to humans.

There are also other terrifying viruses that provoke life-threatening conditions, such as the human immunodeficiency virus (HIV), a retrovirus that causes acquired immunodeficiency syndrome (AIDS). HIV infection leads to immunosuppression, and infected subjects are thus prone to various deadly diseases caused by microbes, including cancers (e.g. Kaposi's sarcoma caused by infection with human herpesvirus 8) and tuberculosis (caused by the bacterium *Mycobacterium tuberculosis*). Thus, without adequate antiretroviral treatment, infected individuals succumb to AIDS. Importantly, there are individuals that are resistant to HIV infection. The reason for their resistance is an allelic variant of the C-C chemokine receptor 5 (CCR5) gene (11). CCR5 is the main coreceptor for HIV entry into immune system cells during primary infection. Deletion of 32 base pairs from the coding sequence of the CCR5 gene, so called Δ32 mutation, leads to generation of truncated CCR5. As a consequence, CCR5-tropic HIV strains cannot efficiently infect individuals carrying the CCR5 Δ32 allelic variant (11).

This is an extreme example how a modification of the immune system affects the ability of a virus to efficiently infect an individual. In this particular case, aberrant expression of a chemokine receptor is the cause of resistance. There is a growing body of evidence of the role of various chemokine and chemokine receptor polymorphisms in different outcomes after infection with viruses, including HIV, HCV, and West Nile virus (11). Also, polymorphism of other immune system molecules, such as cytokines and pathogen-associated pattern recognition receptors, has an important role in determining the outcome of various infectious diseases

(12-14). Importantly, major histocompatibility complex (MHC) molecules are the most polymorphic genes in vertebrates. It is widely accepted that their polymorphism is very important for the resistance of human populations to infectious diseases (15). Thus, thanks to various polymorphisms that make individuals resistant to microbial infections, the human population is protected from extinction caused by microorganisms.

Why have there been microorganisms that cause high mortality diseases?

From the evolutionary perspective, viruses that cause high mortality in humans are not well adjusted to the host, as high mortality generally leads to inefficacy in viral spread. Thus, these are viruses or their variants that have recently been introduced into a human population. The story of smallpox and humans is one of the most striking examples of high mortality due to the human populations' viral inexperience. Smallpox is caused by the Variola virus that is supposed to have evolved from a variola-like rodent virus in Africa some 16,000-68,000 years ago (16). It is proposed to have emerged in Africa, to have spread to India, then to China and later to western Asia and Europe. The lethality of smallpox was extremely high in populations that had not co-evolved with the virus, i.e. in populations whose ancestors were not affected by the virus. For instance, the fatality rate in the Japanese population in the 8th century was around 33% (17). Even higher mortality has been attributed to native Americans in the 16th century, when the virus came to the New World with the Europeans.

Smallpox and other infectious diseases had a devastating effect on native populations, as 90% of Americans are thought to have died of these diseases (17). One of the major reasons for such susceptibility of native Americans to smallpox was that their ancestors left the Old World before the Variola virus affected human populations there. Unlike Europeans, that had been affected by smallpox for centuries, native Americans were not. Thus, instead of the peak lethality of approximately 30% that was observed in the Old World, lethality in native Americans was much higher. As has already been said, not only smallpox, but also other diseases, such as influenza and measles, were more deadly to Americans, whose populations were not previously exposed to these diseases. It has been estimated that some 500 million people lived worldwide and some 60 million in America at that time. More than 10% of humans were therefore native Americans. Contemporary demographic data show that native Americans now contribute to the worldwide human population in a minute proportion of less than 1%. Thus, this is an extraordinary example of the demographic influence of infectious diseases in human populations. Smallpox is the first communicable disease to be eradicated worldwide, thanks to vaccination. Now imagine that the possibility existed to perform vaccination in native Americans in the 16th century. The human population and civilization as we know it would almost certainly look quite different.

Is it possible to have a symbiotic relationship with a pathogenic microbe?

There are good examples which show that viruses that cause mild or no symptoms are very successful in spreading through human populations, either horizontally or vertically. For instance, the prevalence of human papillomavirus (HPV) has been estimated at 30-50% in individuals of 15-60 years of age. Although there are HPV types that are highly cancerogenic, such as HPV 16 and 18, it seems that the majority of some 40 types are benevolent to humans. Even recognized can-

cerogenic types do not present an equal treat to all humans, as infection with these types does not necessarily lead to tumorogenesis. It is proposed that human populations and HPV types have co-evolved in a way to prevent cancerogenesis (6). It seems that cancers arise when evolutionarily mismatched human and viral genotypes are paired. Indeed, it was shown that non-European subtypes of HPV 16 are the most tumorogenic to European women (6). The rationale behind a mild or no viral effect on the host is as follows: integration of the HPV genome into the human genome is permanent and the inability of the host to have sexual contact with other individuals as a consequence of damaged health or even death is a dead end for the further spread of that particular HPV. Thus, it is in the best interest of the virus to cause no or little harm to the host, in other words to move away from parasitism towards commensalism. But, are there pathogenic viruses that make an additional step from commensalism to symbiosis?

There are clues that cytomegalovirus (CMV) could be considered symbiotic to humans, at least at a certain age of the host and in certain aspects. CMV is a herpesvirus that infects the majority of human populations worldwide (18). Primary infection with CMV is usually asymptomatic and followed by a lifelong latent infection. From time to time, reactivation of CMV occurs, yet again it is mostly asymptomatic (18, 19). However, the latent infection has been proposed to cause various changes in immune system functions, including modulation of the ratio between naïve and memory T cells and T cell effector functions (19). Although CMV latency is generally considered pathogenic and supportive to immunosenescence, it has been proposed that the latency up-regulates the basal activation state of innate immunity against subsequent infections (20). Also, CMV infection has been correlated with a better outcome of influenza vaccination (21). Interestingly, CMV infection has been associated with expansion of highly polyfunctional $CD57^+$ T cells which confer better protection against other microorganisms (19, 22). Thus, it seems that CMV might even be considered a symbiotic organism that protects the host from other infections.

This tendency towards a symbiotic relationship is not limited to viruses. The bacterium *Helicobacter pylori* is another example of shifting from pathogenicity to symbiosis during the course of co-evolution. This bacterium chronically infects the gastric epithelia of approximately 50% of humans worldwide. Some 10-20% of the infected individuals suffer from peptic ulcer, and 1% develop distal gastric carcinoma (23, 24). Still, the majority of the infected individuals suffer from relatively mild gastritis and, due to the presence of *Helicobacter pylori* within their gastrointestinal tract, they are protected from various diseases, including esophageal cancer, reflux esophagitis, diarrhea and even childhood asthma (25-27). Importantly, *Helicobacter pylori* is transmitted in a vertical fashion, and genetic compatibility between the host and the bacterium is supported in this way (6). Having this in mind, as well as the long period of co-evolution with humans (estimated at 50,000 years), it seems that life-threatening clinical diseases should not be expected from this bacterium (6). Yet, as already stated, they do occur and they are likely to be the consequence of genetic incompatibility between the host and the bacterium. As *Helicobacter pylori* is inherited from the mother, this incompatibility might be the consequence of the father's genetic influence. Also, having in mind local co-evolution, the spread of *Helicobacter pylori* specific for one geographical area into another may also account for the incompatibility (6).

Does vaccination shift the balance between pathogenic microorganisms and humans?

Although the plasticity of the human immune system allows us to assume that no virus or any other kind of pathogen will ever be able to eradicate humans, individuals are vulnerable to many microorganisms. Depending on the infectious disease, the proportion of individuals that succumb will differ from minor to major, and thus there will be a stronger or weaker influence on the human population in general. Prevention, *i.e.*, vaccination, is the right way to save individuals and, if properly conducted, to eradicate diseases. There are numerous pathogens that are exclusive to humans, such as those that cause smallpox, measles, mumps, rubella, falciparum malaria, poliomyelitis, syphilis and AIDS. Therefore, if proper vaccination is performed, these diseases will be eliminated. Unfortunately, the only disease that has been eradicated so far is smallpox. For some pathogens, no efficient vaccines have yet been produced. However, even for those for which efficient vaccines are available, eradication has not been realized due to various political and social reasons (28).

One of the good examples for the effect of vaccination on the relationship between a pathogen and humans is the HPV vaccine. As already explained, HPV is in a relative evolutionary balance with human populations. Still, due to the ever increasing mixture of various human populations, evolutionarily mismatched human and viral genotypes are paired, thus increasing the risk of cancerogenesis in individuals. Therefore, the production of efficient vaccine against HPV is a necessity. There are 13 HPV types that are designated as human carcinogens. HPV 16 and 18 account for 70% of cervical cancers worldwide. Also, HPV 6 and 11 are responsible for 90% of genital warts (29). Therefore, a nonavalent HPV vaccine that protects against diseases caused by HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58, a quadrivalent HPV vaccine that targets HPV 6, 11, 16 and 18, and a bivalent HPV vaccine against HPV 16 and 18 have been produced and recommended for application in young females and males. If applied properly, this vaccine will surely shift the balance from malignant HPV types towards benign ones.

Conclusion

Having in mind that this issue of The Central European Journal of Paediatrics is dedicated to vaccination, my final remarks in this paper will be devoted to vaccination as well. If we talk about microorganisms that are almost exclusively fatal to humans, there is no doubt that vaccination is contributing to the survival of human populations in a major way (Fig. 1). Therefore, research towards the generation of vaccines for HIV, Ebola and other devastating diseases is among the most important areas of study in biomedicine today. The above examples also illustrate that some of the microorganisms that have been considered as strict pathogens might actually have beneficial effects on their hosts. In other words, the same microorganisms might have detrimental or beneficial effects in different individuals. This is very important for planning a vaccination and antibiotic treatment approach, *i.e.*, large scale eradication *vs*. individual treatment. Thus, a better understanding of our co-evolution with pathogenic microorganisms, at both genetic and physiological levels, is necessary for designing adequate vaccination strategies. Vaccination, as a revolutionary approach in co-evolution of humans and pathogenic microorganisms, must be designed carefully for each of the pathogens. Once a vaccine has been shown to be safe and effective, vaccination should be applied to the whole population, as this is the right way to shift the balance with pathogenic microrganisms to our benefit.

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