

## Co Evolution of Man and Microbial Pathogenic Genome

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### Abstract

**Background:** Co-evolution of human and microbial genome is of fundamental interest. It allows both the human and pathogens to adapt themselves in the changing environment. Even in an experimental condition to check resistance against a particular antibiotic the microbes slowly develop resistance against that antibiotic in laboratory environment. Thus it is a very critical issue that should be address in order to overcome the microbial diseases. Purpose: The present study is focus on the currently evolved pathogens and availability of vaccines; that work against the pathogens to protect human population. Conclusion: By understanding the way pathogens get evolved will be helpful in future to develop new and more affective vaccines. It may also helpful in understanding the disease pathogenesis.

**Keywords:** Co-evolution; Environment; Pathogenic genome; Pathogenesis; Vaccines

### Introduction

Evolution is actually a change that develops over in successive generation; these changes are basically in the inherited material that is DNA and proteins. Evolution give rise to diversity and makes the generation more suitable to the changing environment [1]. Cosmologists believe that the universe began some 14 billion years ago with the gigantic 'primordial fireball' called the Big Bang. The early Earth was covered with water and it was in this vast planetary ocean that the first biochemical systems appeared, cellular life being well established by the time land masses began to appear, some 3.5 billion years ago. But cellular life was a relatively late stage in biochemical evolution, being preceded by self-replicating poly nucleotides that were the progenitors of the first genomes. In the very early history of earth the oxygen content were very low, until the process of photosynthesis evolved, the other gases that are present in the atmosphere were probably methane and ammonia. These two gases also produce a range of amino acids, including alanine, glycine, valine and several of the others commonly found in proteins. Hydrogen cyanide and formaldehyde are also formed, these participating in additional reactions to give other amino acids, as well as purines, pyrimidines and, in less abundance, sugars. Progress was initially stalled by the apparent requirement that polynucleotides and polypeptides must work in harness in order to produce a self-reproducing biochemical system. The nucleotides and polypeptides are linked together in random to give rise the first complete biochemical system. The most important step in the genome evolution is the synthesis of enzymes. Since then it has been sought that every life form is unique. Behind genome evolution there are many driving forces, gene duplication, recombination, mutation and several randomized events. Co-evolution of human and pathogenic microbes has been the topic of interest for many years. Co-evolution is a dynamic process: if host and pathogen co-evolve, then a 'functional' gene in one time and place may be a 'non-functional' gene in another time and place. Failure to recognize the dynamic nature of the interaction could result in misinterpretation of its genetic basis. That pathogens and hosts have evolutionary effects on one another and that these effects might be reciprocal; that is, pathogens and hosts co-evolve are attractive, plausible and powerful ideas whose implications for the medical and veterinary sciences are only just beginning to be recognized [2].

Co-evolution as it is the process of reciprocal, adaptive genetic change in two or more species [3,4]. This simply means that changes in gene frequencies as a result of selection acting on one population create selection for changes in gene frequencies in the other population(s),

although the kinds of population genetic processes that result can be different, as we detail below. Co-evolution can occur between any interacting populations: prey and predator, plant and herbivore, competitors or mutualists; but it is expected to be particularly important in host-pathogen systems because of the intimate nature of the association and the strong selective pressures that each can exert on the other [3,4]. Co-evolution requires (i) genetic variation (additive genetic variation for diploid species) in the relevant host and pathogen traits (ii) reciprocal effects of the traits involved on the fitness of the two populations and (iii) dependence of the outcome of the host-pathogen interaction on the combinations of genotypes involved (in multi-locus systems, this makes epistasis and linkage disequilibrium potentially important). There are several ways in which pathogen species interact within a host. At one level, pathogens may simply compete for host resources, and so directly influence each other's fitness. This may include sharing, and competing for, the same host receptors. Environmental as well as genetic factors will inevitably influence host-pathogen interactions and, particularly among vertebrates, there is the further complication of phenotypic plasticity [5]. The most obvious example is the adaptive immune response, which allows the same genetic machinery to be used to combat a vast number of different pathogens. And, in humans and perhaps other species, behavioral plasticity may also ameliorate the impact of pathogens. Here in this study our major focus will be on pathogen and human co-evolution and complication arise due to the evolution.

### Rate of Genome Evolution in Pathogens

Successful evolution leads to a successful life is the result of many factors. Several factors are involved in pathogenic microbes' evolution. These factors and/or mechanisms are point mutations, genetic rearrangements and lateral gene transfer processes contribute to the evolution of microbes. Long-term processes leading to the development of new species or subspecies are termed macroevolution,

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and short-term developments, which occur during days or weeks, are considered as microevolution. Horizontal gene transfer is the fundamental mechanism involve in microbial pathogenic evolution. Among macro and microevolution the later type is more fundamental, it results in the production of change phenotypes, play an important role in the acute development of an infectious disease. Mutation rates in bacteria are generally in the range of 10<sup>-6</sup> to 10<sup>-9</sup> per nucleotide per generation. Bacterial evolution requires shifting from old functions to the new functions. Pathogens face a hostile and often novel environment when infecting a new host and adaptation is likely to be an important determinant of the success in colonization and establishment. It has been experimentally demonstrated that host immune system that cause resistance to infection impose a selection on pathogens that can infect the host. Thus host immune system is one of the major factors that drive evolution in pathogenic microbes [6]. Other factor that has been studied is mutation and the environmental influence on the selection of mutation [7]. Rapid evolution put light on how the pathogenic microbes overcome the host defense system. Rate of evolution is different in different viruses and bacterial families. Host environment also influence the rate of transformation [8]. Amino acid substitution is another factor that causes changes in gene and genome expression. The proportion of substitution can be use directly to estimate the rate of evolution. So, it has been concluded that substitution of amino acid is correlated with adaptive evolution of pathogens [9]. Pathogenicity islands were also found to play important role in pathogenicity of pathogenic bacteria; their length differs in different bacterial species [10].

### Rate of genome evolution in Human

The rate of genome evolution is low in human as compare to pathogens due to large genome size, long generation time and relative abundance of non coding regions. Human beings have been evolved in relation to pathogens with the generation of large number of different antibodies that recognized specific pattern of pathogenic microbes and neutralized them. The major factors behind the evolution and variation in human genome are the diversity of local pathogens and selection pressure that is governs by the environment [11].

### Evolution of Human immune system

Human immune system also called the defensive system that provides both innate and adaptive protection against pathogens. Human immune system provides this defense by producing antibodies and macrophages and T and B lymphocytes. Human defense system is one of the most rapidly evolving systems. As soon as a pathogen encounters the human inner body cell, it starts producing antibodies that neutralize or sometimes destroy the pathogenic component of bacteria. It has been demonstrated that changes in cultural traditions, economical and social status along with population growth and agriculture are affecting nutritional values of human worldwide. Thus affecting the microbiota and human immune system on the whole. Every life form competes with other lives in order to survive. As said by Aldous Huxley "That men do not learn very much from the lessons of history is the most important of all the lessons that history has to teach." So, every time a pathogen encounter with a host, host develop immunity against that pathogens, this is what is called co-evolution of host and pathogens. It has been estimated that about 20 to 50\*10<sup>6</sup> pre-B cells produced daily in animal model. Due to presence of V-D-J component of heavy and V-J component of light chain through the process of random joining produce vast diversity of antibodies that express a variety of epitope binding site. Thus the rate of evolution is very high in B cells [12]. Different types of T cells also produce in the body, like effector T cells, memory T cells. However the rate of

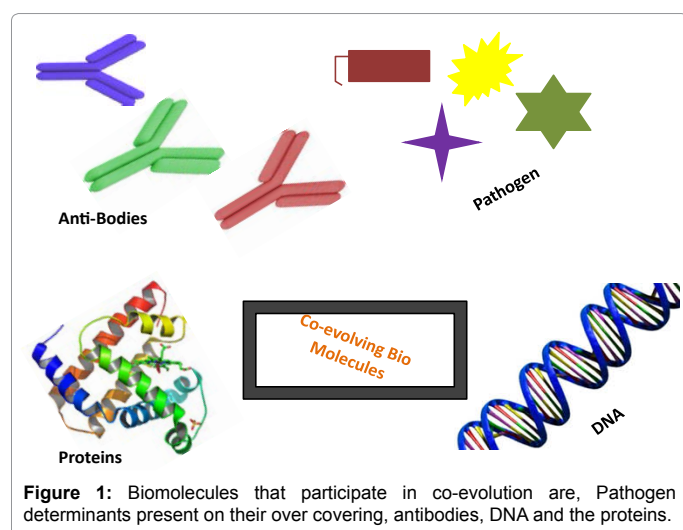
proliferation of memory B cells is much more than that of memory T cells [13].

### Co-Evolution of human and pathogens

Human and many parasites have been found to co evolved over millions of years. Human has evolved so as the disease causing microbes also evolved. Different diseases are appeared and disappear this is due to the fact human changes in human and pathogens. Human has evolved to deal with pathogens or to make themselves resistant towards pathogens, whereas pathogens evolved to evade themselves from host immune system [14]. It has been studied that in case of tuberculosis, both human genetic evolution and bacterial evolution plays a critical role in the spreading of the disease around the globe [15]. It was demonstrated that some chronic pathogens become less pathogenic through the process of host-pathogen co-evolution. Thus co-evolutions greatly influence the pathogenicity of human pathogens [16]. Immunity and infection are the two component of society that moves side by side. Human leukocytes antigens are the most divergent and polymorphic component. HLA has main function in adaptive immunity they present antigen peptides to the T cells and B cells [17]. Comparative genomics a new era in molecular biology open new doors, it also clearly indicates that both human and pathogen genome coevolved. Bacterial evolution started long before the emergence of animals. In fact, bacteria were the first, and for some time the only, inhabitants of Earth. Therefore, early evolution involved competition, genetic exchange, and selection only between bacteria [18]. As human moves through the most modern genetic era, different types of more pathogenic microbes also evolved. Human body contain microbes more than their own body cells, although these microbes are stable but they still prone to cause serious disease as the rate of horizontal gene transfer is high in microbes, this makes the previously non pathogenic bacteria to become pathogenic. The microbes reside inside the body also gives strong evidence that both microbes and human co-evolve. As human ecology changes so, as the microbiota, then only those microbes survives who have positive impact on host. The development of antibodies perhaps one of the major cause of evolution in microbes, the change their recognition site for their survival [19].

### Bio-molecule co-evolution

Host-pathogens are in a continuous race of evolution, host develops different mechanisms to protect themselves from pathogenic infection whereas pathogens on the other hand develop mechanism to cut off the defense of the host. Horizontal gene transfer is the fundamental mechanism through which pathogens microbes becomes more powerful. This phenomenon occurs only when two different DNA are close enough that sharing occur. Once the DNA inserted, DNA stabilized itself into the new organism, gene rearrangement and modification took place [18]. Thus the interaction between two or more individual; causes them to change their genetic material in relation to the time and requirement is called co-evolution. Mostly host maintain their genetic polymorphism in relation to the interacting pathogens however; genetic variability occur in order to defend itself from invading pathogens [20]. Human being have relatively slow reproductive rate due to huge amount of hereditary material as selection of partner as compare to the microbial pathogens that through the process of asexual reproduction give birth to thousands of individual in relatively short time. Thus bearing the beneficial mutation that provides shield against harmful pathogens becomes less possible for human. The other fact important factors behind slow evolution of human genetic system are that most of the pathogens do not affects the host reproductive system. Understanding the host-pathogen biochemistry is primary resource to



start with it. Environmental as well as genetic factors unavoidable in host pathogen co evolutionary pressure. It has also been studied that the interaction of pathogen is multipotent and or polygenic rather than simple gene to gene interaction. So, understanding such a complex interaction becomes extremely difficult. There are number of reasons for which the pathogen interacts with the host, they may require host resource, they may aim to disturb the host fitness or they may wants to overcome the host machinery to make it useful for their own purposes. Polymorphism and the positive selection of the changes are the hall mark of evolution. In case of pathogens the polymorphic alleles are present only on antigen specific genes such as glycoprotein and lecithins encoding genes [21]. Biomolecules of the host and pathogens are not negligible in this regard of co-evolution. It was studied that antimicrobial peptides are the major source that provides defense against pathogens. Although the defense provided by these antimicrobial peptides is one of the ancient type of system, but this system found to be evolved in relation to the pathogens [22]. The following figure 1 show some of the bio-molecules involve in driving the co-evolutionary process fast.

### Co-Evolution at population level and Biomolecules level

Co-Evolution is a fundament aspect that has been studied both at population level and Biomolecules level to control the infectious diseases. If a both these level studied jointly they put more light on how and why co-evolution occur? The species that lived in a particular geographical area becomes more adapted and specialized as compared to other related species residing other areas. The raw material for the overall process of co-evolution is the genes that transfer from one organism to the other organism through the local interaction. This ultimately results in the flow out of genes from that particular geographical area to the nearby areas. A highly virulent form of microbe infects a population results in the extinction of that host population and also its own extinction. Some populations with time develop powerful resistance genes results in the extinction of deadly virulent microbe only. The third situation may also arise in which both host and virulent pathogenic microbe co-evolved [23]. A population gets evolved due to fitness requirement; a particular population wants to get more fit to the environment as compare to its remote population. The major potential force behind this evolutionary process is migration, mutation and recombination. The power of evolution is much more in pathogenic microbial population as compare to the host population due to their relative short generation period, large number and high rate of polymorphism and mutation. The selection and variation are the paramount of the process of evolution

[24]. In the absence of these forces of evolution the populations are considered at Hardy-Weinberg equilibrium. A reciprocal change in the genome of two closely interacting species is the main pillar of co-evolution. Thus it can be concluded that the fundamental element of co-evolution is reciprocity. That is the change in one specie cause the change in the other species [25]. The study of co-evolution at molecular level is the most recent trend basically depends upon the evolution of protein families and protein-protein interaction. At molecular level co-evolutionary changes are the fundamental driving force behind evolutionary changes. Protein-protein interaction (PPI) and the relationships of protein family with similar functionality are basal for understanding co-evolution. Co-evolution at species level was done by Ehrlich [26]. As co-evolution occur in species living together in close proximity and interacting with each other; this interaction forms the basis for the study at molecular level [27]. For the study of co-evolution different approaches are used and polished up till now for more and more improvement. One of the elementary approaches that have been used both at specie level and molecular level is phylogenetic tree analysis. On the other hand, although the phylogenetic profiles were originally designed to contain information at full-sequence level, profiles based on domain presence/absence successfully predicted domain interactions [28]. Profile-profile similarity has been calculated using different metrics such as euclidean distance [29], mutual information [30] or Hamming distance. Co-evolution has also been observed at residual level, where only a single amino acid and/or even a single nucleotide change that cause frame shift also significant. Thus the accumulation of these mutations at residual level plays a significant role in co-evolution. Ligand-receptor interaction so called PPI can be estimated with the help of tol-mirror tree as compared to the original mirror tree [31]. Co-evolution was also found between the mitochondrial-encoded rRNAs of the mitochondrial ribosomes and the nuclear-encoded proteins of these organelles [32]. A similar strategy based tree-similarity was used to study the co-evolution between the nuclear- and chloroplast-encoded members of the RuBisCO protein complex [33]. Co-evolution-based approaches, together with other computational approaches which also use sequence and genomic information for inferring protein linkages, form a family of approaches termed “context-based methods” [34], which complement the classical homology-based methods in obtaining information on different aspects of the proteins from their raw sequences [35]. Co-evolution is not a well understood process, only by observing species and the cause that pushing them towards evolution will helps to put insight in this phenomenon.

### Impact of Co-evolution

Co-evolution is strictly an interaction base phenomenon. The change in one species is triggered by changes in the other closely interacting specie. The modulation and up gradation in host genome for the sake of protection from pathogens trigger the evolution in pathogen genome and make them more pathogenic. The human-parasite co-evolution is one of the fundamental relationships to study the impact of co-evolution on both human and parasite genome. The genome of both organism changes through the reciprocal pressure of selectivity. The unique relationship of host-parasite was also explained by RED QUEEN hypothesis [36]. According to that hypothesis “it takes all the running you can do to keep in the same place”. Co-evolution is a pervasive event of potential importance in living organisms. Many medically dangerous diseases are caused by co-evolved pathogens. Human and pathogen interaction has strong impact on pathogen strategy to attack on human and in case of human it has impact on the adaptation in host immune system. Virulence (the tendency of a pathogen to cause damage to a host's fitness) evolves when that pathogen can spread from

a diseased host, despite that host being much debilitated. An example is the malaria parasite which can spread from a person near death, by hitching a ride to a healthy person on a mosquito that has bitten the diseased person. This is called horizontal transmission in contrast to vertical transmission, which tends to evolve symbiosis (after a period of high morbidity and mortality in the population) by linking the pathogen's evolutionary success to the evolutionary success of the host organism. Evolutionary medicine has found that under horizontal transmission, the host population might never develop tolerance to the pathogen.

### Paradigm of human-pathogen co-evolution

To study evolutionary events for organisms with long generation is slow and difficult process. In case on human-pathogen co-evolution the host immune system evolved somehow more rapidly as compare to overall generation time of the host. Pathogens due to their small size, short generation time, a-sexual mode of replication and the phenomenon of horizontal gene transfer are more adaptive to the changing host conditions. There are number of factors that affect the phenomenon of co-evolution. Among these factors environmental factors are not negligible. Some human immune system and pathogens likely to co-evolve along different trajectories in different locations likely to be co-evolve along different trajectories in different locations. Organism having short generation time and a combination of both sexual and a-sexual mode of replication produces offspring in larger varieties and numbers. Table 1 shows the list of pathogens that are currently present in the population and found harmful.

All these microbes along with hundreds of thousand microbes are still need to be listed. Against all these microbes vaccines are available and these vaccines could be the reason of evolution in pathogens. Although the vaccines are available but the infections due to these

pathogens are still present in the human population. This is just because of the fundamental process of co-evolution. By clear understanding how the process does occur we will be able to understand how a particular microbes get variation and then we can immediately start working on booster or more potentially effective vaccines without wasting our time and resource on the study of why variation occur?.

### Co-evolution of Bordetella pertussis with respect to the Host

Bordetella pertussis (B. pertussis) is one the causes of whooping cough disease and cause many deaths in newly born babies. Although the vaccines are available, that could prevent patients from this harmful disease. The first vaccine was developed based on whole cell vaccine. In which complete cell of B. pertussis was employed, although it had effective control over the disease symptoms but it also evoked serious side effects as the strains are able to revert. Until 1997 whole cell vaccines was used as it produced robust immunity in the recipient but the side effects are nasty. The first vaccine against pertussis was developed in the 1930s. A new acellular vaccine against B. Pertussis was developed that contain one of the protein coding domain that produces a key surface protein Pertactin. Pertactin is one of the three proteins, made from purified extracts of B. pertussis bacteria, which are present in the vaccine currently used in Australia. The other two are pertussis toxin and filamentous haemagglutinin. In a study conducted by a UNSW-led team of researchers analysed strains of B. pertussis from across Australia and found that many strains no longer produce a key surface protein called pertactin. This protein may be the cause of evolution in these bacteria. The efficacy of vaccines which was previously 84 % to 85 % now decreasing day by day due to conformational changes in the surface proteins [37]. Thus it can be concluded vaccination could have significant reduction, but B. pertussis produces several new strains that evade from vaccines. There is a need to device new vaccines that should conjugate with some immune provoking component. So, that

Serial No.	Name of pathogen	Type	Disease cause	Vaccine available or not	Reference
1	<i>Mycobacterium tuberculosis</i>	Bacterial	tuberculosis	Yes	Ottenhoff 2012
2	<i>Streptococcus</i>	Bacterial	pneumonia	Yes	CDC 2013
3	<i>Pseudomonas</i>	Bacterial	pneumonia	Yes	CDC 2013
4	<i>Shigella</i>	Bacterial		Yes	Barry, 2012
5	<i>Campylobacter</i>	Bacterial	food poisoning	Yes	Lisa, <i>et al.</i> , 2013
6	<i>salmonella</i>	Bacterial	Typhoid fever	Yes	Zhang S 2013
7	<i>Yersinia pestis</i>	Bacterial	Black plague		Devender 2011
8	<i>Variola</i>	Virus	Smallpox	Yes	Damon IK 2014
9	<i>Infuenza</i>	Virus	Flu	Yes	Lanying, 2010
10	<i>Malaria</i>	Protoza	Malarial fever	Yes	Noe AR <i>et al.</i> , 2014
11	<i>Clostridium tetani.</i>	Bacterial	Tetanus	Yes	Skariyachan S, <i>et al</i> 2013
12	<i>Corynebacterium diphtheriae</i>	Bacterial	Diphtheria(Respiratory track illness)	Yes	Adkins I, <i>et al.</i> , 2012
13	<b>Syphilis</b>	Bacterial	sexually transmitted infection, cause mental illness	Yes	Cameron, Lukehart, 2014
14	<i>Mycobacterium leprae</i> and <i>Mycobacterium lepromatosis</i>	Bacterial	Laprosy	Yes	Duthie <i>et al.</i> , 2014
15	<i>Bodettela pertussis</i>	Bacterial	Whooping Cough	Yes	Weiss, <i>et al.</i> , 2004
16	<i>Helicobacter Pylori</i>	Bacterial	Gastritis	Under clinical trials	Anderl & Gerhard, 2014
17	<i>Hepatitis virus</i>	Viral	Hepatic disease	Yes	Belousova, 2014
18	<i>Polio virus</i>	Viral	Polio	Yes	Jacob John <i>et al.</i> , 2014
19	<i>Acquired immune deficiency virus</i>	Viral	AIDs	Yes	Shearer <i>et al.</i> , 2014
20	<i>Dengue</i>	Viral	Dengue fever	Yes	Maria Rosario Capeding <i>et al.</i> , 2014
21	<i>Chlamydia pneumoniae</i>		Alzheimer's	Yes	Li Y <i>et al.</i> , 2010
22	<i>rhinovirus</i>	viral	Asthema	Yes	Blanco <i>et al.</i> , 2014
23	<i>E. coli</i>	Bacterial	diarrhoea	Yes	Ahmed T <i>et al.</i> , 2013

**Table1:** List of pathogens, disease cause by these pathogens and available vaccines status.



it could boost up the immune response against vaccine. The major cause of behind the evolution of *B. pertussis* is acellular vaccines and environmental factors along with the need to live for bacteria.

### Co-evolution of *Mycobacterium tuberculosis* and Human

*Mycobacterium tuberculosis* is the causative agent of tuberculosis. Dr Young and his team used high-throughput DNA sequencing techniques to analyze the whole genomes of 259 strains of *M. tuberculosis*. They concluded with that *M. tuberculosis* have adapted to the changes, as human evolve through the microbes also do the same. It is present mostly in pulmonary cavities, empyema pus, or solid caseous material, where penetration of antibiotics is difficult or the pH is sufficiently low to inhibit the activity of most antibiotics [38]. The *M. tuberculosis* has little opportunity to interact and exchange genetic information with other strains. The resistance can occur through chromosomal mutation although rarely movement of mobile genetic elements also seen [39]. Genomic studies also revealed that there is a wide variety of *M. tuberculosis* genus. Many of which are multiple drug resistant [40]. TB is the prototype of a disease of poverty [41]. The human TB appears to be significantly older than approximately 10 000 years is supported by several additional lines of evidence. A recent study from Turkey reported a 500 000 year old fossil of *Homo erectus*, which shows lesions characteristic of TB [42]. As the changes due to evolution are difficult to see in human however to find out such evolutionary changes are more significant and promising in pathogens. Thus it can be inferred from findings that evolution of pathogens is according to its host lineage [42]. The study of co-evolution of TB and human is of great interest; it helps to understand the disease pathogenecity and level of preventive measures. Population, causing gastric inflammation and, in a small percentage of patients, stomach cancer—the second leading cause of cancer-related deaths worldwide. But the prevalence of *H. pylori* infections do not correlate with cancer incidence, suggesting other factors are at play [43].

### Co-evolution of *H. Pylori*

*Helicobacter pylori* is a dangerous and widespread bacterium that resides and makes colonies in the gut mucosa in nearly half the human population. It is the cause of gastric inflammation that may leads to stomach cancer is small amount of patients. *H. pylori* is the second leading cause of cancer-related deaths worldwide. But the prevalence of *H. pylori* infections do not correlate with cancer incidence, there are a number of other factors that play their role in disease pathogenesis. The researchers around the world provide evidence that those other factors include the ancestry of both the host and the pathogen; patients that are infected with *H. pylori* strains that have a distinct ancestry from their own are more likely to suffer severe disease.

Curious about the role of co-evolution between these populations and their pathogens many researcher investigated sample from *H. pylori* infected patients. In the end, the researchers found that while all *H. pylori* sampled showed evidence of multiple ancestries, those in the coastal region, with a low incidence of stomach cancer, were dominated by ancestral African makeup, just like their human hosts. Those in the mountain region, on the other hand, where gastric cancer is more common, appeared to be more closely related to *H. pylori* of southern Europe, unlike the predominately Amerindian human population. The results suggested that a shared evolutionary history of humans and bacteria resulted in a less virulent host-pathogen relationship [44].

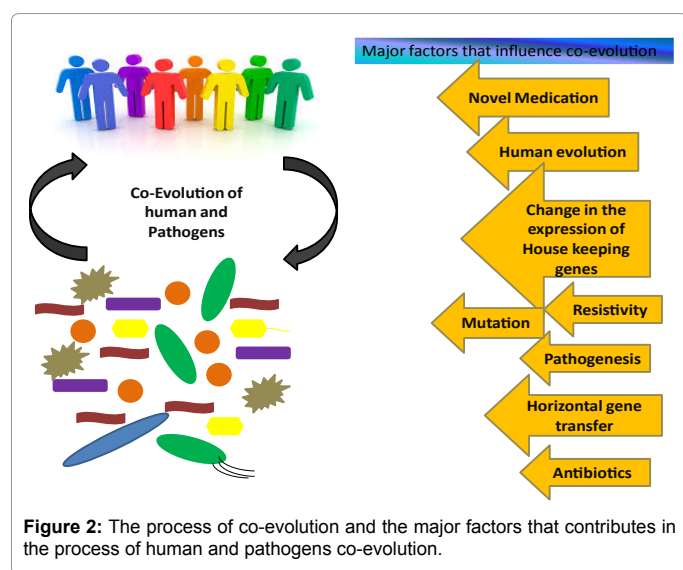
The story of co-evolution keeps getting more and more interesting and more and more complex. It will require more dedicated studies to unfold the whole story. As the phenomenon of co-evolution is still far from understanding clearly.

### Importance of Co-evolution

As discussed so far, co-evolution of human and pathogens is a Co-evolution is a pervasive event of potential importance in living organisms. Host pathogen relationship is powerful determinant for the understanding the biology and genetics bases of human/host and pathogen. Host-parasite coevolution is a ubiquitous phenomenon of potential importance to all living organisms, including humans. Many medically relevant diseases (e.g. malaria, AIDS and influenza) are caused by coevolving parasites. Therefore detailed understanding of the coevolutionary adaptations between parasite 'attack strategy' and host immune system may result in the development of novel medications and vaccines and thus help save human life [45]. The process of co-evolution of human and pathogens still need to be understand, as the phenomenon of co-evolution is complex and important subject; especially since man is the only animal who has been capable of changing host conditions in a rapid manner by evolutionary standards. A major element of pathogen evolution appears to have arisen during the mid to late Holocene, as urbanization began. One theory is that for certain zoonotic diseases, faunal reservoirs kept human affecting pathogens alive; a competing, but not mutually exclusive theory is that mutations of human pathogens arose, and were maintained as opportunities for close contact increased in urban settings; before this area of large, dense human population, certain pathogens may not have had an opportunity to thrive. This urbanization hypothesis helps in explaining why disease transmission was chiefly in the direction of Europe to the Americas [46]. Where more urban societies were settling into less densely populated cultural areas [47]. In certain pathogens, genes normally carrying out housekeeping functions may adopt new functions, whereas in other organisms, genes that respond to stresses associated with non-host environments are silenced during infection to prevent the expression of products that interfere with the normal colonization process. The adaptive behavior of certain pathogens relies on gene variation at certain loci that by virtue of containing polymeric repeats in regulatory or coding regions can generate variants that may or may not express products that modify the cell surface of the organism. Thus co-evolution also put light on the process of gene regulation, when and which gene should be regulated in order to stabilize the population of pathogens in the host [48].

### Take home message

Co-evolution is a reciprocal adaptive genetic change in two interacting species. These adaptive changes are occur due to environmental selection pressure, mutation, duplication, gene conversion and above all the pressure impose by pathogens on their host and resistance against pathogen in the host. Every living being is composed of four DNA base, the changes are just in the sequence and the arrangement of these four bases. In case of human; pathogen recognizing receptor goes through evolutionary changes and become more adaptive for the upcoming pathogens. Whereas the pathogens get evolved by expressing new and different components that help them to evade host immune system. Different studies have been carried out but the exact purpose of co-evolution is far from understanding. Studies revealed that co-evolution is the basic requirement for the maintenance of food chain and the ultimate plant earth. Many genetic and bioinformatics tools helps in the demonstration of the process of co-evolution. Still there is an urge to find out evolutionary purpose of two interacting species. As this will shed light on how to prevent a particular disease, what type of affective vaccines could be produced in future and what is the role of human immune system regarding to the diversity and evolutionary pressure of the pathogens. The figure 2 show some of the major factors that influence the co-evolutionary process.



Thus it can be concluded with that by knowing all the factors that derive the process of co-evolution in two closely interacting species that have infection resistant relationship can be understood and will be helpful in future in disease diagnosis and perspective what could be the modification in a particular organism that cause it to escape from the host immune system. The story of co-evolution keeps getting more and more interesting and more complex. It will require more dedicated studies to unfold the whole story. As the phenomenon of co-evolution is still far from being understood clearly. If the process of co-evolution is neglected, it can jeopardize the extensive global efforts done so far to eradicate the deadly diseases from this world.

Thus by understanding the way by which human gets evolved due to the interaction of pathogens and how the pathogens get evolved rapidly to evade themselves from the human immune system is the current requirement of the co-evolving world of human-pathogens.

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