



# The necessity to revise Koch's postulates and its application to infectious and non-infectious diseases: a mini-review

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## Abstract

Advances in the science have promoted all aspects of human's life; these, in turn, have changed many principles and scientific postulates. Koch's postulates, since the beginning of their implementation, have been one of the important subjects involving complications and misinterpretations regarding the causal relationship of microbe-hosts. These postulates have been shown not to be correct in some cases including the inability of some microbes to grow in the culture medium, viruses, or anaerobic bacteria. Today, due to some new scientific facts like the social behaviors of bacteria, such as quorum sensing, there are serious problems regarding the definition of whole microbial effects; these include microbiomes and viromes, as well as their interaction with the existing eukaryotics, the complicated relations between bacteria, L-forms, and cell wall-deficient bacteria, and the important role of microbes in the development of non-infectious diseases. So, the application of Koch's postulates to explain the causal relationships between host-microbes could be difficult. Therefore, nowadays, even the molecular Koch's postulates are not accountable. Also, according to the new scientific discoveries, various criteria such as changes in the immune system, pathology, and clinical findings, along with the results of daily laboratory tests, should be used to apply Koch's postulates in the etiologic studies. Otherwise, the possible etiologic relationships between the host-microbes cannot be verified due to numerous complications; certainly, the relationship between the doctor and the lab is ultimately weakened. Therefore, public health, prevention, and much of the antimicrobial treatments will also remain in a state of ambiguity.

**Keywords** Koch's postulates · Interpretation · L-form · Biofilm

## Introduction

More than a century has passed since the emergence of the idea of cause and effect regarding infectious diseases according to Koch's postulates. Koch and other leading scientists of modern microbiology have drawn on the theory of the spontaneous generation of infectious diseases, discovering the microbes and discussing the theory of biogenesis for the

production of infectious diseases by four sentences known as Koch's postulates. They have ultimately attributed the incidence of any infectious disease to a microbe. Since that time, because some microbes could not be grown, or there are not animal models for the simulation of certain diseases, in the case of the bacterial carriage of healthy humans, the so-called postulates have been in a halo of darkness [1]. In fact, there is no consensus regarding this subject. Applying these postulates to explain the etiology of some groups of microbes and finding their relation with some human diseases including viruses, intracellular bacteria, and anaerobes have not been easy. After nearly 150 years, the question is whether a scientist can easily use Koch's postulates for the confirmation of the etiology of infectious diseases with microbes. To put it in another way, is it really necessary to draw on Koch's postulates because of eradication or reduction of infectious diseases, as claimed by the health officials? It should be noted that the interpretation and use of Koch's postulates have become complicated due to the modern life, the complexity of the interactions of microbes and immune system, the presence of many cross-linking

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antigens between host-microbes, the increase rate of travels and emerging diseases, improvements in clinical, pathologic, and histological diagnostics, and some complicated infectious forms of bacteria including L-forms, cell wall-deficient bacteria (CWDB), and biofilms (Fig. 1).

## Microbiome and Koch's postulates

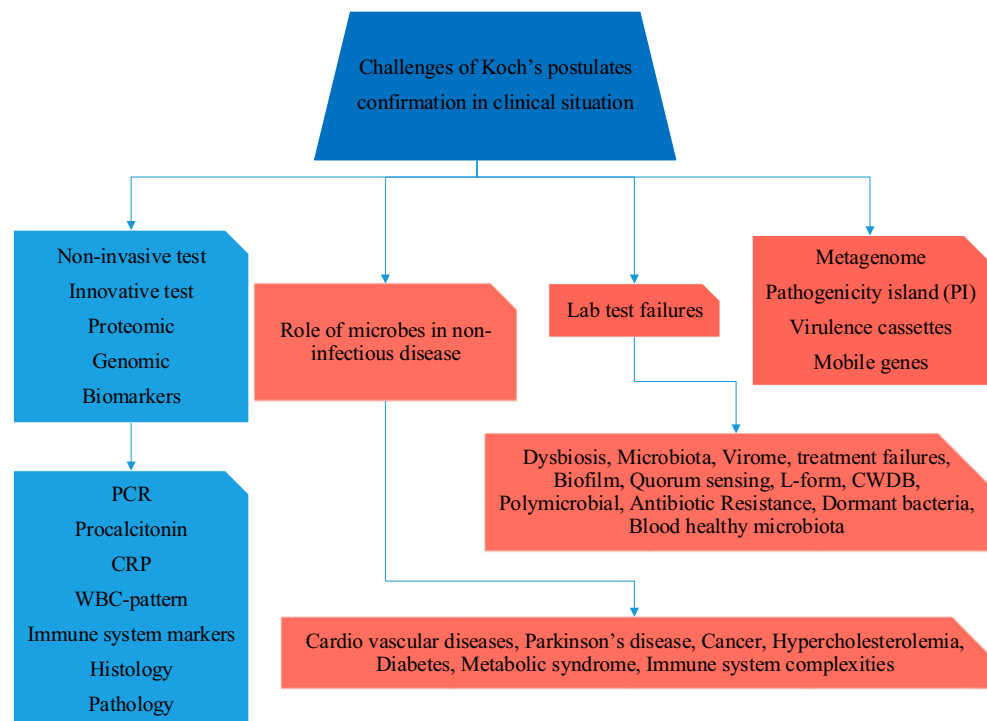
One other recent important conception is the definition of microbiome, virome, and microbial communities, showing remarkable interchanges between microbes in biologic and clinical settings. This further complicates the microbial relations with each other and host organs, so it is almost impossible to interpret Koch's postulates in many diseases.

One of the most recent important issues is the successful cultivation of more than 800 different bacteria from the healthy blood [2]; this can be regarded as a tsunami seriously affecting many principles and practical codes applied to process clinical samples in laboratory. So, Koch's postulates and how they reveal the casual effects of host-microbes should be reexamined. Based on this fact, with the growth of several colonies of n blood cultures, no one can identify the main cause of infection in cases such as bacteremia and septicemia. So, we should develop a model that can conform to new facts in proving the hypotheses presented. That will definitely be the case, and the scientific community of medicine will need to invent new rules to interpret the causes of some infectious diseases.

## The role of microbes in non-infectious diseases and Koch's postulates

In spite of the claims of health officials of the world that many infectious diseases have been eradicated, the role of bacteria and different bacterial forms like L-forms, cell wall-deficient bacteria (CWDB), and dormant bacteria, as mentioned in some diseases including cancer, infarctions, chronic tonsillitis and arthritis, autoimmune diseases, infective endocarditis, rheumatic fever, systemic lupus erythematosus, scleroderma, Crohn's disease, pyogenic arthritis, recurrent osteomyelitis, bone marrow transplants, and idiopathic septicemia, is still unexplored. These can not only decrease the importance of microbes in the human's health and life but also enhance the role of microbes in other life-threatening apparently non-infectious diseases [3–5]. In fact, L-form bacteria have been isolated from many clinical samples [6–10], and they have been produced from more than 50 pathogenic species of bacteria [6–8, 10, 11]. On the other hand, "dormant blood microbiota" have been discussed in some studies as potentially viable (but possibly non-proliferating) pleomorphic bacteria in the blood of healthy individuals [12, 13], which could play a role in the pathology of diseases like atherosclerosis, cardiovascular diseases, and type II diabetes [14, 15]. Even the routine blood culture methods should be revised and re-defined because when we can see hundreds of bacterial viable and non-viable forms in the blood of healthy individuals, standard operation procedures of blood or other apparently sterile samples are not meaningful. Additionally, blood fungal normal microbiota have also been reported in some studies [13], which can make it difficult, if not impossible, to isolate and culture them; so, Koch's postulates

**Fig. 1** Complexity of the interpretation of Koch's postulate in the twenty-first century



may prove to be ineffective in the interpretation of infections etiologies. Therefore, in such conditions, especially for non-infectious diseases that have a microbial origin, the use of Koch's postulates for interpretation needs a full revision; so, talking about one microbe-one disease is impossible in the determination of infections etiologies. In fact, the infectious agents-host relations have been changed like other aspects of life. Production of antibiotic-resistant strains based on the nutritional behavior and inadvertent use of antibiotics or herbal medicines, as well as creeping of cell wall-defective forms in hypertonic or isotonic sites of body as hidden or herpetic forms, with the potential of recurrent infections [4] or immune system-related problems in long-term exposures, is another complication involved in attributing microbes to some infections. Certainly, in the case of L-forms and other complicated bacterial forms like biofilms, confirming the etiology of many infectious and non-infectious diseases and giving information to people and clinicians can be very useful in decreasing the concerns and costs of health that are imposed on the families and health systems all over the world.

## Biofilms and Koch's postulates

The other important medical problem which complicates the Koch's postulates interpretation in this new era is the formation of biofilms and their role in 65 to 80% of all human infections based on the reports from the Center for Disease Control and Prevention [16–18]. Bacteria are commonly found as biofilm phenotypes in their native ecosystems, and they intervene with many chronic infections including wounds and implanted device infections, which are usually resistant to antibiotics [19]. In many cases, the culture of bacteria in biofilms communities including indwelling medical devices related to infections is facing some difficulties; these have been explained in Wolcott's "*biofilm theory*" as *implant infections which need new methods for the successful culture of bacteria in the detection of causes* [18, 20]. In fact, the behavior of bacteria in biofilms is such that they cannot be cultivated by routine methods; on the other hand, using molecular methods cannot solve the problem of detecting the causes of infections, which is mainly because of a cocktail of microbes that can be found as blood or even intraerythrocytic, apparently natural flora. So, in such cases, drawing on Koch's postulates cannot be a scientific and meaningful subject [2, 5, 13]. For example, in the study of Rhoads et al., 17 and 338 taxa of bacteria were identified from 168 wound samples with a routine culture and molecular techniques, respectively [19]. In such a condition, finding principal organism responsible for etiologic studies or doing antibiogram for treatment proposes is almost impossible, even with the application of molecular methods like ribotyping.

Finally, the complicated relations between microbe-hosts and definition of normal blood bacterial, virus, and fungal

microbiomes in the literature as the normal flora of healthy individuals should be taken into account; on the other hand, to investigate the high impact of non-infectious diseases on the human's life with the microbial origin, comprehensive studies are needed to determine the exact role of microbes in such conditions. Therefore, designing new patterns and defining new principles of Koch's postulates, even other than molecular postulates, are necessary to confirm role of microbes in such situations. Therefore, based on these facts, we cannot assign Koch's postulates by simply isolating microbes from clinical samples as the etiologies of diseases; instead, it is proposed that important criteria including count, distribution, arrangement, and species of microbial maps in different ecological niches of body (in health and disease) be prepared for etiologic judgments. In other words, to better judge the etiologic role of microbes in the human diseases, normal and disease microbiome maps of different sites of human body should be prepared, like chromosomal maps for detailed studies. In addition, because of the complicated relations of microbes with hosts, implementing and simultaneously using pathological and immunological patterns of microbial changes in body indexes, like inflammatory, epithelial cells, special inclusion bodies, and microbial direct morphologies, could be certainly useful criteria in tagging Koch's postulates to the infectious and non-infectious diseases.

## Conclusion

Given the role of microbes in non-infectious diseases in the new era and the complicated relations between them, their causal effects can no longer be determined only by isolating or culturing a microbe from clinical specimens. So, according to the information provided, in addition to laboratory microbiological data, the results of clinical, pathological (cell and histological), and even immunologic analysis should be considered in the assessment of the etiology of the diseases. By implementing the new criteria as the modern postulates, the etiology of many unknown infectious and non-infectious diseases could be discovered; this, in turn, can lead to correct treatment and prophylaxis in the future.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This is a literature review study and therefore, ethical approval was not required.

**Informed consent** For this type of study, formal consent was not required.

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