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The Importance and Relevance of Improving Bacteriological Diagnostics in Chronic Infectious Diseases

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Abstract: The current coronavirus epidemic has highlighted the need for a more global approach to human health in a matter of months. Indeed, we will need to alter our approach at the clinical and research levels due to the rapid spread of infectious diseases and their unpredictable effects on human lives and financial losses. In the end, we should be prepared to combat infectious diseases that afflict a vast number of people worldwide. This new situation will call for quick, low-cost diagnostic devices that can be used anywhere in the world and, ideally, don't require specialized staff. Treatments for various illnesses also need to be inexpensive, simple to use, scalable, and adaptable. All of this will only be feasible with the cooperation of the governments, who will need to loosen the standards for the approval of novel treatments. In the meanwhile, the pharmaceutical industry needs to make a commitment to put globally relevant products ahead of the most lucrative ones. Severe situations necessitate a strong reaction, and any future profit losses could prove beneficial. Here, we list the emerging technologies that will address the present and upcoming health issues brought on by infectious diseases and talk about which ones are most likely to be put into practice.

Keywords: globalization, new treatments, diagnostic tools, antibiotic resistance, infectious diseases

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Introduction. The connection between globalization and human health, particularly infectious diseases, is no longer questioned. Different environmental, demographic, technological, and economic factors clearly influence the prevalence, rate of propagation, geographic spread, and control of contagious illnesses. As a result of our world being more interconnected, these are also evolving. For example, the incidence and behavior of infectious diseases are significantly impacted by global environmental change (https://www.who.int/globalchange/environment/en/). Indeed, certain people may be more susceptible to illnesses due to the increasing risks that climate change poses to the world's water supply. In a similar

vein, demographic shifts like population migration and urbanization may hasten the spread of viruses to new regions. It's also critical to take into account how industrialized and developing nations differ in their susceptibility to infectious diseases [1-5]. Beyond the straightforward exchange of commodities and services, changes in the global economy, particularly those pertaining to international trade, have an impact on infectious illnesses because they also affect social welfare and access to a quality healthcare system. Globalization typically results in increased disparities between nations, particularly with regard to access to medical and technical advancements. Public health systems must, however, be prepared to offer an effective hygienic response to both endemic and pandemic illnesses. Developing better strategies for infection prevention, control, and treatment will be necessary to overcome this obstacle. In order to effectively reduce the global illness burden, these new methods will subsequently need to be implemented in all nations. The spread of emerging (new, undiscovered diseases) and re-emerging infectious diseases (endemic diseases with antibiotic resistance), which pose a threat to public health and have major social, political, and economic ramifications, is another effect of globalization [6-11]. Ebola virus (Africa), Middle East respiratory syndrome coronavirus (MERS) (Middle East), Zika, chikungunya, yellow fever, and dengue viruses (North and South America), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (worldwide) are some of the most important infectious agents that have emerged and re-emerged over the past ten years. But the most noticeable infections may distract public health officials from other deadly infectious diseases that might spread like wildfire. Emerging infections are increasing the hazards associated with an aging population in wealthy nations that is more vulnerable to infectious diseases and has chronic illnesses. In contrast, infectious infections exacerbate issues including insufficient financial resources, hunger, and uncontrolled antimicrobial medication use in poorer nations. Many bacterial pathogens, including *Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacteriaceae, Enterococcus faecium, Staphylococcus aureus, Helicobacter pylori, Campylobacter spp., Salmonellae, Neisseria gonorrhoeae, Streptococcus pneumoniae, Haemophilus influenza* and *Shigella spp.*, are developing drug resistance, which exacerbates the situation. Antimicrobial resistance (AMR) is, in fact, one of the major issues facing human health worldwide [12-17]. In addition to improving the diagnosis of infectious diseases, recent developments in fundamental science research and the creation of molecular biology tools have also produced significant information regarding pathogenesis and epidemiology. As a result, science provides the instruments required for effective disease prevention and control. But a new obstacle is now confronting the advancements made in this discipline during the previous century. In order to address global health issues, current methods for diagnosing and treating diseases must be modified. Numerous molecular tests have been created to address pathogen identification and quantification with high sensitivity and specificity in response to this issue. Some nucleic acid-based detection techniques that demonstrate excellent sensitivity, specificity, accuracy, efficiency, and versatility are among them. In general, improved stewardship practices and the development of new, potent antimicrobials will be required to end the vicious cycle of resistance. Additionally, disease risk assessment will assist in determining which areas need more work from the public health system in order to reduce population vulnerability in the near future. Here, we offer a thorough analysis of the studies meant to mitigate the impending dangers of bacterial infectious diseases, particularly those resulting from antibiotic resistance. We also talk about which strategies are more likely to be used in clinical settings [5-14].

The main purpose of this brief review is to analyze the importance and relevance of improving the bacteriological diagnosis of chronic infectious diseases based on the results of reputable scientific research.

Cutting Edge Bacterial Pathogen Diagnostic Tests. The current millennium has seen a shift in the way bacterial diseases propagate. Infectious diseases caused by bacteria, viruses, parasites, and fungus used to flourish in times of conflict and poverty, sometimes killing millions of people in a brief amount of time. Later, while communicable diseases continued to be the leading cause of death in developing countries, they ceased to pose a significant threat in industrialized countries. However, significant epidemics have also surfaced in wealthy nations during the past few decades. Legionnaires' disease, E. coli O157:H7, and

bovine spongiform encephalopathy (BSE), also referred to as "mad cow disease," are a few prominent instances. More recently, the COVID-19 epidemic has drastically affected our lives and, as a result, how we see every facet of infectious illness diagnosis and treatment. In fact, we are now more conscious of the various ways that effective diagnostic techniques might aid in the treatment of these diseases [4-11]. Accurate diagnosis, for instance, can enhance treatment efficacy, aid reduce long-term consequences, stop transmission to others, support appropriate antibiotic use, and even help put an end to an outbreak. However, as new infectious diseases emerge, diagnostic techniques must be modified to meet current demands. This can be accomplished by utilizing the newest technologies to create tests that are simple to use anywhere in the globe and provide a prompt and accurate diagnosis. The following are a some of the primary technologies being developed or utilized in the clinic [12-17].

Culture of Pathogens. The gold standard for diagnosing the majority of infectious disorders is still positive aerobic or anaerobic culture of a potentially sterile fluid (blood, urine, etc.), despite significant advancements in the last ten years in the detection and identification of bacteria. This method's low sensitivity and sometimes lengthy processing times are drawbacks. Furthermore, the use of superfluous antibiotics may result from false-positive cultures, the delayed development of picky bacteria, or the possible growth of commensal microbes. When a positive culture is found, the Gram stain and other stains are typically utilized, along with selective culture plates to test for antibiotic resistance [10,11,12]. Up until 1992, phenotypic identification techniques like API 20E, which could identify nearly 100 taxa, were regarded as the "gold standard." Nowadays, automated versions like Vitek® (bioMérieux, Marcy l'Etoile, France) can shorten the time needed to get findings. Peptide nucleic acid fluorescence in-situ hybridization (PNA FISH), a technique for testing blood smears prepared immediately from positive blood culture bottles that provides results in 2.5 hours, is another time-saving technique. Lastly, it should be mentioned that the identification of certain bacteria requires the use of molecular-based techniques. For example, Mycobacterium tuberculosis can be diagnosed from sputum using multiplex PCR, RFLP, and MAS-PCR, and Mycobacterium leprae can be diagnosed quickly and definitively using Fite–Faraco (FF) staining and PCR [13-17].

Tests Based on Antibodies. Immunofluorescence and latex agglutination make it possible to identify infections in clinical samples rather quickly. For more than 50 years, ELISA assays have been utilized in clinical settings for serological testing and the detection of antigens from infections. The notion of multiplex and multiarray ELISA began to be developed after the DNA microarray technique became available, although very few tests have been validated for in vitro diagnostic (IVD) applications. For this intricate technology to produce reliable and precise findings in clinical diagnostic situations, automation and algorithm-driven design are necessary. Because it can quantitatively identify minute levels of biomarkers, ultrasensitive ELISA has recently been advocated for disease diagnosis. For example, precise identification of the secreted immunogenic protein MPT64 can be used to diagnose active pulmonary M. tuberculosis, enabling appropriate treatment of the illness and additional evaluation of treatment efficacy [1,2,3]. ***Molecular Methods.*** Because of their great sensitivity and specificity, molecular methods have grown in importance throughout time and are now essential in laboratories in industrialized nations. Nucleic acid extraction and multiplex PCR have been incorporated into test cartridges such as FilmArray (bioMérieux) and GeneXpert (Cepheid). Due to the low amounts of nucleic acids seen in clinical samples, conventional techniques like PCR and real-time PCR are unable to identify pathogens that persist in the human body in a latent state of infection (such as tuberculosis). By serially diluting the sample, digital PCR takes use of the PCR's ability to amplify a single molecule and allows for DNA template quantification [5,6,7,8]. In a similar manner, droplet digital PCR counts the final positive results after splitting the PCR mix into tiny reactions that run separately. Research labs and hospitals can now purchase ddPCR devices from Bio-Rad Laboratories (USA), Thermo Fisher Scientific (USA), and RainDance® (Bio-Rad, USA). Multilocus polymerase chain reaction (PCR) and electrospray ionization mass spectrometry (PCR/ESI-MS) can be used to examine isolated colonies or unculturable microorganisms. Therefore, a signal for testing is provided by the presence of pathogens in the clinical sample following housekeeping gene amplification. Based on this technique, Abbott Molecular's

IRIDICA offers a variety of platforms for the identification and detection of 130 viral species, 200 molds and yeasts, 780 bacterial and Candida pathogens, and the presence of four specific antibiotic resistance markers [9,10,11].

Transplantation of Faecal Microbiota. The significance of the microbiota in human health is now widely recognized. In reality, a large number of cases demonstrate a connection between the microbiota status and certain diseases. Furthermore, it has been demonstrated that the use of probiotics and fecal microbiota transplantation can lessen the frequency and severity of certain bacterial infections, particularly those that are more challenging to treat or brought on by bacteria that are resistant to antibiotics, like Clostridium difficile. Additionally, specialized genetic engineering of probiotics is made possible by synthetic biology. The effectiveness of probiotics for disease prevention has not yet been thoroughly established, despite encouraging outcomes from controlled trials. Fecal microbiota transplants, on the other hand, have been demonstrated to dramatically counteract the tendency for colonization with multiresistant infections and restore the gut microbiota in patients [3-7]. ***Transplanting bacteriophages.*** It is theoretically feasible to utilize bacteriophages to modify the microbiota because they interact dynamically with the microorganisms that colonize the human gut. Bacteriophage transplants can be used to achieve this result. Although research on this subject is still in its early stages, studies conducted in animal models have shown that phage predation affects the quantity of vulnerable bacteria and, indirectly, other bacterial species, with observable effects on the gut metabolome. Additionally, there is proof that bacteriophages remain and have an effect on human long-term microbial dynamics following fecal microbiota transplantation [11-15].

Dicussion. The connection between globalization and human health, particularly infectious diseases, is no longer disputed. Numerous environmental, demographic, technological, and economic factors clearly influence the prevalence, rate of propagation, geographic spread, and control of contagious illnesses. As a result of our increasingly globalized society, these are also evolving. For example, infectious illness incidence and behavior are significantly impacted by global environmental change (https://www.who.int/globalchange/environment/en/). In fact, some people may be more susceptible to illnesses due to the increasing risks that climate change poses to the world's water supply. Future Difficulties. The WHO has provided the "ASSURED" definition of the ideal diagnostic test (Affordable, Sensitive, Specific, User-friendly, Rapid, Equipment-free, and Delivered to those who need it) due to the significance of diagnostic systems in preventing the spread and minimizing the harm of infectious diseases at a sufficiently early stage. However, despite the creation of many tests in recent years, there have been few studies evaluating their effectiveness in real-world contexts, particularly in low-resource areas and regulatory systems [1,3,4,5]. Choosing the right kind of clinical sample to use for detection is one of the issues related to test development. Samples should be simple to gather, process, and store because unqualified workers may use diagnostic tests. The requirement to first extract genetic material, which is often done by hand, is another disadvantage of the majority of molecular techniques. In terms of sample processing, it would be ideal for the POC to cover every step required to get results, particularly under biosafety-restricted conditions and when the samples are highly contagious. However, in order for any diagnostic test to be used in nations all over the world, it must be simple to handle and inexpensive. Clinical trials necessitate screening a huge number of individuals, which makes the approval and commercialization of these treatments more challenging, among other reasons [9,10,11]. Personalized medication is more expensive per patient, which makes it less available in developing nations. In this regard, immunization against infectious diseases is crucial in lowering the prevalence of certain ailments in these nations. Since phage products may be generated more quickly and at a lower cost than traditional pharmaceuticals, inexpensive treatment options like phage therapy may be a useful option in this situation. In general, improved stewardship practices and the development of innovative, potent antimicrobials will be required to end the vicious cycle of resistance. Additionally, illness risk assessment will assist in determining which areas need more work from the public health system in order to reduce population weakness in the near future. Here, we offer a thorough analysis of the studies aimed at mitigating the impending dangers of bacterial infectious diseases, particularly those resulting from

antibiotic resistance. We also discuss which strategies are more likely to be used in clinical settings [12-17].

Conclusions. The development of antibiotic resistance in the current century has undermined the advancements in human medicine, particularly in the fight against infections, that resulted from the discovery of antibiotics in the twentieth century. The involvement of multiple disciplines is crucial to overcoming this disadvantage. Therefore, studies related to the environment and epidemiology are important for designing containment mechanisms; veterinary science is important for preventing animals from acting as carriers and reservoirs of resistant pathogens; public health is important for managing surveillance and controlling the development of resistance; medicine, immunology, and pharmacology are essential for the logical design of new therapies; and, finally, molecular biology and chemistry will contribute to the advancement of our understanding of disease etiology and pathogenesis.

Drug discovery and treatment design against the majority of pathogens are being aided by the gathering of fundamental knowledge from omics (genomic, transcriptomic, proteomic, and metabolomics) data. Beyond that, a global sociopolitical effort will be needed to handle the global control and transmission of specific illnesses. Therefore, governments and international organizations will play a critical role in the control of infectious diseases. The advent of new and/or more virulent viruses and changes in other elements (social, political, environmental, technological, and environmental) that facilitate their transmission make infectious illnesses a persistent issue despite the tremendous advancements accomplished. This fact necessitates ongoing monitoring, intervention, and the use of appropriate technologies to aid in diagnosis and treatment.

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