

THE MEDICAL AND EPIDEMIOLOGICAL SIGNIFICANCE OF CONDITIONALLY PATHOGENIC MICROORGANISMS AND THE RELEVANCE OF OPTIMIZING CONTROL MEASURES**Dilafroz Sh. Gulmurotova
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Abstract. Millions of individuals have been infected by the COVID-19 pandemic, which has resulted in a public health emergency and a considerable number of fatalities. It is challenging to stop SARS-CoV-2 from spreading throughout the community since it can transfer from person to person through a variety of channels, primarily respiratory droplets. An summary of COVID-19's epidemiology, etiology, clinical presentation, diagnosis, and treatment is given below. Based on the widely held belief that customizing interventions, practices, and/or therapies to each patient's unique clinical, biological, epidemiological, and genetic characteristics would maximize their efficacy and minimize side effects, personalized medicine has been gradually incorporated into a number of diagnostic and therapeutic patient algorithms. Recently, the precision medicine approach's potential advantages have been examined for prospective application in the field of infection prevention and control. The coronavirus has spread quickly due to direct person-to-person respiratory transmission. The present clinical therapy of COVID-19 consists of symptom management, infection prevention and control measures, optimized supportive care, and intensive care support in cases of severe or critical disease because there are currently no clinically established treatment options. Nowadays, creating a successful vaccination is a top scientific focus. The regulatory bodies have already authorized a few vaccines to prevent COVID-19. The opinion examines the information that is currently available and evaluates potential future scenarios in which we might be able to deliver personalized prediction algorithms that identify at-risk patients who should receive customized preventive treatments using sophisticated modeling techniques. To reduce the danger of infection, general prevention and protection measures pertaining to the containment and control of the second or third waves are required. Two vaccines (Pfizer/BioNTech and Moderna) have acquired FDA emergency use permission, and four vaccinations have demonstrated varying efficacies ranging from 62 to 95% thus far. Millions of lives will be saved if these vaccines are distributed effectively and have equitable access in every nation.

Keywords. COVID-19, SARS-COV-2, pathogenesis, clinical manifestations, diagnosis, treatment, hospital transmission, infection control, customized treatment.

Introduction. With the main objective of lowering infection rates, infection control refers to the policies and practices created to restrict and reduce the transmission of infections in hospitals and other healthcare settings. The United States officially recognized infection control in the early 1950s. A few hospitals started to identify healthcare-associated infections and put some infection control measures into place by the late 1950s and early 1960s. In order to improve patient outcomes, this exercise examines the various infection control techniques and their indications, emphasizing the interprofessional team's responsibility in upholding infection control principles. Based on the widely held belief that customizing interventions, practices, and/or therapies to each patient's unique clinical, biological, epidemiological, and genetic characteristics would maximize their efficacy, personalized medicine, also known as precision medicine, has been gradually incorporated into a number of diagnostic and therapeutic patient algorithms for noncommunicable diseases [1-6]. In the setting of three main determinants—lifestyle, comorbidities, and genetic and epigenomic profiling—oncology is the medical specialty where this idea has been widely used to treatment and preventative initiatives. Cite Boussios, Esteller, Moran, and Martinez-Cardón. During the Coronavirus Disease 19 pandemic, clinical data combined with genomics and molecular technologies were used to identify etiologic agents, develop diagnostics and treatments, and develop vaccine candidates. This is a recent example of personalized medicine application in the field of infectious diseases. Cite Collins and Denny. The precision approach's potential advantages have lately been taken into consideration for prospective application in the field of infection prevention and control (IPC). Gonzalo, Harris, and Tacconelli are cited, as is Gastmeier. Implementing a measure, or a combination of measures, specifically in individuals deemed at-risk based on patient-related (epidemiology, comorbidities, omics profile) and pathogen-related (molecular resistance mechanism and/or virulence factors) determinants would be the ideal objective of precision IPC. In addition to optimizing the effectiveness of the implemented measure, the ability to accurately quantify the risk of horizontal transmission at the individual level in colonized and/or infected patients may also reduce negative effects (such as decreased contact with healthcare workers, organizational constraints due to single room isolation), hospital staff workload, and hospital expenses [7-12]. Simultaneously, the decreased burden may result in better adherence to therapies, which could further limit horizontal transfer between patients and/or healthcare professionals. Whether containment methods are evidence-based and effective is a key question in this study. Since there aren't many overt laboratory-acquired illnesses (LAIs), one may argue that the evidence supporting the efficacy of containment strategies is, at most, indirect. Furthermore, we can wonder if the standards used to assess efficacy are adequately defined. In fact, the goals of containment measures are frequently not clearly stated, and it is challenging to assess their efficacy in the absence of (quantifiable) goals. Additionally, evaluating the quality of the evidence is crucial while searching for proof of the efficacy of biosafety measures. For comparison, in evidence-based medicine, systematic reviews, hypothesis-driven controlled laboratory experiments, and prospective studies provide a higher quality of evidence than case reports and expert opinion. In this review, we will define the present biosafety practice, provide a brief historical account of its development, and attempt to pinpoint the methods and ideas that seem to underpin it. After that, we outline a method for assessing how well biosafety measures work to keep pathogenic microorganisms contained [13-20]. Lastly, we provide an overview of observational and experimental evidence about the efficacy of containment techniques. Evaluating evidence-based GMO containment strategies is our main objective. However, we also look at evidence-based strategies to contain non-GMO diseases because these strategies are mostly based on containment strategies for non-GMOs and because there is more data—albeit

limited—available for non-GMOs. It is possible to extrapolate these findings to GMOs. In doing so, we seek to add to a conceptual framework that supports the advancement of an evidence-based biosafety approach. Providing a thorough grasp of developments in the microbiome-host connection for human health is the aim of this review. With an emphasis on multiomics techniques and the cellular reprogramming of microbes to enable thorough microbiome research and robust microbiome engineering, this Review also attempts to provide a nonexhaustive list of studies covering the manipulation of the human microbiome to prevent or treat human disease [21-28].

The main purpose of the presented manuscript is to provide a brief overview of the results of reputable scientific papers on the medical epidemiological significance of opportunistic pathogens and the relevance of optimizing control measures.

Over the past few decades, microbiome research has advanced quickly, and it is currently a topic of enormous scientific and public interest. In the past, environmental microbiome study gave rise to the area of microbiome research, which subsequently developed the idea that eukaryotes are inextricably linked to the microbial population they coexist with. Ultimately, the human body is an ecosystem in which the host coexists with trillions of microscopic species. Therefore, the collection of genes from all microorganisms that live in nearly every region of the human body is referred to as the "microbiome" in science. As a result, the microbiome is seen as a second genome that coexists harmoniously with the host. Microbiome interactions are important for human health because they can be either positive or beneficial, negative or pathogenic, or neutral. With an estimated 50–100 times more genes, the diverse and intricate microbiome functions as a functional extension of host genomes. By having different kinds of enzymatic proteins, these additional genes influence the metabolites that are created, which in turn affects host metabolism and helps regulate host physiology [1-5]. Over time, a holistic approach based on the holobiont theory has been used in place of examining the interaction between a single bacterium and its host. While disease development is frequently associated with microbial dysbiosis, or a change in the microbiota, the host's health is maintained by the beneficial interaction of the host with its microbiome. As a result, pathogens only make up a very small portion of microorganisms, and their appearance and breakout are facilitated by the microbiome's altered composition. In addition to their beneficial interactions with other microbes, which contribute to population dynamics and functional activities, the great majority of microorganisms are essential for ecosystem functioning. Opportunistic pathogens thus demonstrate that host-microbe interactions are dependent on both the host and the overall microbiome. All biological components that make up the microbiome—which includes bacteria, fungus, algae, archaea, and tiny protists—are referred to as the microbiota. One of the most contentious additions to the notion of a microbiome is the inclusion of viruses, phages, and mobile genetic material. Since then, however, the term "microbiome" has been expanded to include not just the community of microbes but also the entire range of chemicals produced by bacteria, including their structural components, metabolites, and compounds produced by the coexisting host. Microbial makeup typically differs between various anatomical regions, and it is extremely individualized because each person's microbiome is unique [6-13]. Although the precise definition of a healthy microbiota is still unknown, research has demonstrated that taking probiotics, prebiotics, and synbiotics can help maintain a healthy body flora or change the microbiome in the direction of a healthy microbial ecology. Determining the core microbiota is therefore essential because it makes it easier to distinguish between an intermittent or temporal microbiome that is impacted by particular environmental factors. While transient microbiota varies over time, core microbiota is the

microbial population that is consistently linked to a particular host genotype or environment. The strategy used in microbiome investigations for medicinal applications can be improved by recognizing these differences and applying a suitable experimental, methodological, and statistical design [14-19].

A short historic overview of containment measurement development. A. G. Wedum of the U.S. Biological Research Laboratories at Fort Detrick, MD, can be considered one of the pioneers in creating biosafety measures following World War II, even though Robert Koch had already created some form of biosafety cabinet (BSC). He assessed the dangers of working with dangerous biological agents and created procedures, tools, and facilities to prevent them. Since his early research, it has become widely accepted that ventilation and containment of contaminated work environments are crucial components in the eradication of LAIs. Primary barriers (personal protective equipment and safety equipment) and secondary barriers (facility safeguards) are now considered essential components of containment measures in addition to safe microbiological approaches. Early on, it was realized that analyzing LAIs could provide insight into the dangers associated with laboratory work. As a result, numerous thorough evaluations of LAIs have been created. Laminar-flow BSCs were developed as a result of these early investigations, which identified aerosol as the main mode of transmission for many of the causal chemicals. The risk of occupational exposure to infectious organisms has likely decreased but not completely disappeared as a result of laws and regulations that have been implemented over time [5-13]. Concern over the possible risks connected to recombinant DNA research and technology grew as DNA manipulation became more feasible in the middle of the 1970s. While GMOs may exhibit the desired characteristics, they may also have unforeseen and undesired traits. There seems to be ongoing discussion on the environment's exposure to potentially dangerous genetically modified organisms, as well as the health and safety of laboratory personnel and animals. General guidelines for handling possible GMO-related biohazards were developed during the Asilomar Conference in 1975. It was proposed that containment should be a crucial factor in the design of the experiment and that its efficacy should be commensurate with the projected danger. Infection could be avoided without unreasonably hindering operations by adjusting the level of precaution to the level of risk. The National Institutes of Health's (NIH) standards for DNA molecule research were first published in 1976. Three decades later, the safe handling and manipulation of dangerous biological agents, including genetically modified organisms, is governed by a number of authoritative international guidelines, instructions, and recommendations. The first edition of the handbook *Biosafety in Microbiological and Biomedical Laboratories*, published in 1984 by the U.S. National Institutes of Health and the Centers for Disease Control and Prevention (CDC), is today regarded as a key reference work [21-26]. The NIH/CDC and WHO guides, which have been established and enhanced over the past 30 years, are based on historical reports of infectious microorganism occurrences and the vast expertise of professionals working in this sector. For instance, national regulations and the European Union have both established legislation. Directives from the European Union, such as the directive on the contained use of GMOs and the directive on the protection of workers from dangers connected to exposure to biological agents at work, have served as the foundation for national authorities' legislation throughout Europe [28-31].

Personalized IPC's current uses. However, in terms of viability, sustainability, transferability, and the caliber of the available data, the process of personalizing IPC is quite difficult. Recent research that challenges and reevaluates the general application of contact precautions (CP) for inpatients with multi-drug resistant germs (MDROs) outside of the

outbreak scenario has raised the topic of how to appropriately apply precision medicine to IPC. Patients colonized or infected with extended β lactamase-producing Enterobacterales (ESBL-E) are the subject of the most advanced discussion. With the exception of *Escherichia coli*, where there is insufficient data to draw evidence-based conclusions in high-risk patients, the current IPC guidelines strongly advise the use of CP in endemic settings for inpatients colonized or infected with ESBL-E, Reference Tacconelli, Cataldo, and Dancer. Cite Cataldo, Dancer, and Tacconelli More recently, a 2023 comprehensive analysis of nine research (including one with a randomized design; see Reference Maechler, Schwab, and Hansen⁹) revealed that there is no advantage to using contact over routine precautions when it comes to hospital transmission of ESBL-E [6-14]. However, because of the significant variation in colonization pressure between wards, healthcare workload organization, hospital structure, IPC compliance, and population type, these results should be interpreted with caution in terms of generalizability. For instance, none of the studies focused on high-risk environments, and nearly all of them were carried out in endemic regions where the community reservoir—particularly for *E. coli*—was likely the main source of transmission. The availability of data on colonization status and, consequently, the choice of whether or not to implement IPC measures are closely linked to the screening policies (e.g., timeliness, universal vs. targeted groups). The topic is complex because the screening has both an IPC value and a clinical relevance that provides crucial information to support, for instance, surgical peri-operative antibiotic prophylaxis (PAP) or empiric antibiotic therapy in high-risk populations (Reference Micozzi, Gentile, and Santilli). In fact, endogenous flora is the primary cause of most post-operative surgical site infections (SSIs), and a number of observational studies have established a connection between illness and patients' own microbiota. Cite Martin, Gaskins, and Filson [17-22]. Through a variety of processes, including food competition, the generation of antimicrobial compounds, the maintenance of the integrity of the gut barrier, the deployment of bacteriophages, and interactions with the immune system, the gut microbiome can mediate colonization resistance against a number of enteric pathogens. Ducarmon, Zwittink, Hornung, van Schaik, Young, and Kuijper are cited. Asymptomatic gut microbiome-mediated colonization resistance is less relevant for ESBL *E. coli* than other MDROs, according to new multi-omics microbiome analyses. As a result, microbiome-based therapies may not be the best strategy to stop intestinal colonization of ESBL *E. coli*. Cite Zwittink, Willems, and Ducarmon [25-31].

Clinical Importance. In clinical practice, infection control refers to the prompt detection and containment of infections in order to stop their spread. By spotting symptoms and indicators of a transmissible infection, like tuberculosis, clinicians contribute significantly to infection control. To stop the potential spread of the infectious virus, precaution orders must be issued and put into effect even before a confirmation diagnosis is made. In clinical settings, a successful infection control program reduces infection rates and the likelihood that multidrug-resistant bacteria would emerge. One of the most frequent healthcare issues is hospital-acquired infections. As a result, basic safety measures like hand cleanliness can work wonders. One of the best and least expensive ways for physicians to adhere to infection control guidelines is to wash their hands both before and after every patient engagement [5-12]. Therefore, hospitals should actively encourage hand hygiene by placing reminders at each patient's bedside and making sure that sinks or hand sanitizer stations are available at each patient's room entrance. Teaching patients to constantly block their coughs and sneezes with their forearms is another easy step. By doing this, droplet transmission and direct hand contamination—which can spread infections to adjacent surfaces—are avoided. During the COVID-19 pandemic, the clinical importance of infection control was particularly brought to light. Managing a highly contagious

respiratory virus highlighted the vital significance of infection control strategies, such as early detection, isolation procedures, and strict cleanliness standards. Healthcare systems have to quickly adjust to the COVID-19 transmission dynamics, placing more of an emphasis on patient screening, contact tracing, and personal protective equipment [16-23]. Additional measures, such as airborne precautions for patients suspected of possessing COVID-19, became standard during this period. Hospitals have seen personally how successful these measures can be in lowering rates of transmission, but they have also seen how quickly illnesses can spread if safeguards are not regularly taken. The pandemic made it even more evident how important it is to maintain vigilant watchfulness, communicate guidelines clearly, and work together to prevent infections. The pandemic brought to improvements in infection control techniques and technology, including contactless monitoring devices, telemedicine, and the usage of sophisticated ventilation systems in medical facilities [26-31].

The situation of the future. Longitudinal sampling of a patient's changing microbiome to identify pathogens likely to spread could be the foundation of a futuristic, customized implementation of IPC measures. This would allow for a dynamic modulation of IPC throughout the entire hospital stay, with potential benefits from an antimicrobial stewardship standpoint as well. In the case of hematological patients and those having colorectal or transplant surgery, when ESBL-E colonization typically precedes infection, the assessment of the microbiome may be very crucial for making decisions. As previously mentioned, the precision approach at the microbiological level should also take into account whether the presence of particular resistance mechanisms, like AmpC β lactamase vs. OXA-48 carbapenemase, would have a role in the selection of IPC measures. However, the data in this regard is quite weak. From a microbiological perspective, resistance mechanisms like OXA-48-type carbapenemases are frequently found on the same plasmid that can also spread to other bacterial species, albeit these mechanisms can be carried by many plasmids. For instance, OXA-181 and OXA-232 are linked to ISEcp1, Tn2013 on ColE2, and IncX3 types of plasmids; as a result, clonal dissemination contributes very little to the spread of OXA-48-like carbapenemases [6-14]. Furthermore, the plasmid containing the resistance gene is not always linked to the virulence characteristics linked to the efficacy of transmission. Cite Willmann, Sommer, and Hamprecht²⁴. Given these features, a number of variables may affect the probability of infection and transmission, and the identification of the resistance mechanism by itself is currently not thought to be adequate to guide IPC selection. In the context of translational medicine, omic-based methods can also be used to identify the composition of each individual's microbiota and tailor IPC measures accordingly. The customized strategy would need to integrate results from clinical investigations, modeling data, cost analysis, and fundamental research in order to optimize its performance. The implementation of patient-centered IPC measures based on a precision approach is urgently needed; we are undoubtedly not there yet, but we could get closer to this goal than anticipated if we encourage translation research in the IPC sector and integrate it with machine learning data-driven models [18-23].

Discussion. We looked at the data that is currently available regarding the efficacy of policies designed to safeguard people and the environment from the dangers of dealing with both non-GMO pathogenic microorganisms and genetically modified microorganisms (GMOs). Risk assessment, biological containment, concentration and enclosure, exposure minimization, physical confinement, and hazard minimizing are some of the concepts and techniques that underpin modern biosafety practices. Experience and professional judgment are the foundation of many modern procedures. The efficacy of biosafety measures can be assessed at the level of individual containment equipment items and procedures, at the level of the entire laboratory, or

at the clinical-epidemiological level. There is a dearth and fragmentation of information regarding the containment efficacy of laboratories and equipment. A variety of dynamic microbial communities that live in different body anatomical sites make up the human microbiome. As a result of the microbiome's coevolution with the host, these communities have a significant impact on advancing human health. As a result, a number of diseases can be brought on by or made worse by changes in the human microbiome. With an emphasis on the microbiomes present in the skin, digestive, respiratory, urinary, and reproductive systems, we describe our current understanding of the connection between human health and the development of disease in this Review [4-12]. We also go over a number of methods that can be used to alter the human microbiome's makeup and function in order to treat the host. Lastly, we look at technologies that can lead to important developments in microbiome research and engineering, like cellular reprogramming of microorganisms and multiomics techniques. We also discussed how spatiotemporal regulation in engineered microorganisms using synthetic genetic circuits is made possible by common design ideas in synthetic biology that are borrowed from engineering domains. The viability of spatiotemporal regulation within the microbiome environment was demonstrated by certain research that were conducted in the gut microbiome, despite the fact that the majority of them were conducted *in vitro*. Work with GMOs and harmful microbes is governed differently in many nations, including the Netherlands. We suggest harmonizing, modernizing, and streamlining the regulatory framework by creating a single set of rules for both GMOs and non-GMOs because the regulations are based on the same fundamental principles, employ the same biosafety tools, and there are very few GMO-related accidents. There has been a lack of adherence to biosafety procedures in numerous cases of LAIs. If such biosafety procedures are adhered to, this finding would be comforting in terms of their efficacy. It demonstrates that training laboratory staff and adhering to regulations continue to be of utmost importance [15-23]. The annual rate of LAIs per person may have decreased as a result of increased focus on these factors. However, in most LAI cases, a direct cause could not be identified, indicating that containment may have been insufficient or that a failure was often overlooked. This finding might call for more investigation into the exposure pathways in these situations as well as the efficacy of interventions. Lastly, even while tracking LAIs is crucial for assessing how well containment strategies are working, it might ignore the dangers of nonreplicating agents, such transduction by nonreplicating viruses. Therefore, laboratory-acquired infections (LAIs) are crucial for assessing biosafety's efficacy. There doesn't seem to be a clear reason for most LAIs, which may indicate that containment was insufficient or that biosafety issues were overlooked. Compared to non-GMOs, there are much fewer recorded laboratory incidents with GMOs. The degree to which particular actions contribute to the overall level of biosafety is unknown. As a result, we advise strengthening the biosafety practice's evidence base [25-31].

Conclusions. As previously stated, synthetic biology and functional meta-omics techniques aid in overcoming the obstacles impeding the viability of tailored microbe therapy. However, since synthetic biology developed separately from microbiome research, experimental instruments still need to be particularly adjusted for researching the microbiome. As a result, the majority of tools on the market are made to allow *E. coli* to function under continual laboratory settings. There are currently little or no defined genetic components for the nonmodel commensal microbiome. For example, the genetic components of *E. coli* were initially created for *in vitro* use; as a result, the majority of their functions in microbiome environments have not been well assessed and may result in the loss of robustness in genetic

circuits. Because individual microbiomes are diverse, a robust design is essential for medicinal applications.

Therefore, advancements in *in vitro* platforms like organs-on-a-chip and organoids are expected to hasten the optimization of genetic components and gene circuits for *in vivo* contexts. It is frequently unclear to what degree the existing set of particular biological or physical containment methods, either alone or in combination, contribute to the prevention of transmission of harmful germs or genetically modified organisms, despite their apparent overall efficacy in guaranteeing biosafety. Therefore, we advise creating evidence-based procedures and standards to assess efficacy wherever it is practical and viable in order to further develop and modernize the biosafety practice. This could improve and even streamline upcoming biosafety protocols and encourage adherence to regulations.

The evidentiary base for biosafety measures may be strengthened by scientific study, but this kind of work is difficult and does not always provide fresh discoveries that can serve as the foundation for subsequent advancements. Mathematical modeling, which focuses on quantitative parameters of infectivity and transmission, may be helpful in deciphering complexities and gaining additional insight into the contribution of particular elements to biosafety, but modeling clearly requires validation by observational and experimental findings. However, this strategy can highlight the information required to better direct the creation of evidence-based risk assessment and containment strategies for both GMOs and non-GMO infections.

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