Philosophy of Medicine
Perspectives

From Evidence-Based Corona Medicine to Organismic Systems Corona Medicine

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Abstract

The Covid-19 pandemic has challenged both medicine and governments as they have strived to confront the pandemic and its consequences. One major challenge is that evidence-based medicine has struggled to provide timely and necessary evidence to guide medical practice and public policy formulation. We propose an extension of evidence-based corona medicine to an organismic systems corona medicine as a multilevel conceptual framework to develop a robust concept-oriented medical system. The proposed organismic systems corona medicine could help to prevent or mitigate future pandemics by transitioning to a bifocal medicine that extends an empirical evidence-based medicine to a theory-oriented organismic systems medicine.

1. Introduction

The coronavirus disease 2019 (Covid-19) pandemic has not only challenged both medical science and healthcare systems in multiple ways—from the technological and practical to the empirical and theoretical—but also governments and their agencies as they have struggled to formulate public policies to confront and manage the pandemic and its consequences. The challenges are many, including (1) providing sound quality science on the virus itself and its impact on the host's respiratory and immune systems; (2) treating patients safely, effectively, and efficiently with repurposed or innovative drugs; (3) practical measures for reducing or eliminating the transmission of the virus, such as masking and social distancing, as well as reaching herd immunity through vaccination; (4) informing and advising government agencies on how best to formulate public policies; and finally (5) motivating and mobilizing the public to participate in these policies.

One of the major challenges associated with the Covid-19 pandemic is that evidence-based medicine (EBM), which "is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" (Sackett et al. 1996, 71), simply cannot be conducted rapidly enough in terms of randomized clinical or controlled trials and translated directly into actionable clinical practice or into public policy

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(Carley et al. 2020; Greenhalgh 2020). In other words, "follow the science"—or better yet, "follow the evidence"—is just too simplistic and problematic a mantra for confronting and managing the pandemic, particularly in terms of public policies (Mercuri 2020; Stevens 2020). In contrast, because of the rapid dynamics of the pandemic many of the public health regulations were based mainly on expert opinions and not on randomized clinical trials (Pfaff and Schmitt 2021). Also the extension of EBM to EBM+ was recommended; the latter includes knowledge about "mechanisms" in making clinical decisions (Russo and Williamson 2007; Clarke et al. 2013; Parkkinen et al. 2018). However, this recommendation has also been criticized, especially with regard to the treatment of Covid-19 patients, since mechanistic explanations can be wrong, treatment effects can be proven without mechanistic knowledge, and even mechanistic explanations as an additional source of evidence can be misleading (Solomon 2021). We agree and argue that mechanistic knowledge and explanations are often overly reductive and therefore fail to include a systems theoretical context.

What has emerged during the Covid-19 pandemic is a corona medicine (CM) stifled by the challenges facing EBM, which we call EBCM. By CM, we mean both the medical research—predominantly virology and epidemiology describing the pandemic—and the clinical practice of treating individual patients suffering from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We contend that what is urgently needed to avoid or mitigate future pandemics, and possibly other public health crises, is an extension from EBCM, which reduces complexity, to an organismic systems CM or OSCM, which embraces it. A systemic perspective of the corona crisis could enable us to understand the pandemic at the population level (for example, eco-social systems theory) as well as at the individual level (for example, systems pathophysiology).

To that end, we first examine the response of EBCM to the pandemic and the challenges it has faced over the last several years. Part of the reasons for those challenges is predicated on several implicit theoretical assumptions of EBM, particularly reductionism and linear dynamics (Beresford 2010; Nunn 2012). Specifically, EBCM implicitly assumes a reductionist approach, focusing predominantly on biochemical mechanisms as sufficient for treating patients with SARS-CoV-2 infection and for stemming or halting the transmission of coronavirus without considering psychosocial conditions (Fairman 2022). Another assumption of EBCM is that the pathology associated with the viral infection can be adequately accounted for through linear dynamics, especially with respect to causal mechanisms (Greenhalgh, Ozbilgin, and Contandriopoulos 2021). Although such assumptions are necessary for identifying several key components responsible for the pandemic and its impact, they are insufficient for developing a differentiated and robust public health system to respond to the current pandemic and to prevent or mitigate future pandemics and other possible public health crises.

To address these challenges, we propose an organismic systems approach to CM founded on Ludwig von Bertalanffy's organismic biology and systems theory, which integrates the biological, psychological, social, and ecological factors of Covid-19 (Tretter 2019). Specifically, OSCM transcends EBCM's reductionist approach by assuming a holistic approach to the complexity of disease and health, as well as being person centered (Marcum 2015). It also embraces both personal health and public or global health, as well as planetary health, especially in terms of integrating various levels of the pandemic system. OSCM, then, involves medical knowledge integration that captures the diversity of practical, empirical, and theoretical medical disciplines and their historically developed interrelations (Tretter and Löffler-Stastka 2019).

In sum, the proposed organismic systems medicine provides a conceptual framework to develop a robust medical and public health system that can prevent or at least attenuate future pandemics by extending the focus from an EBCM that incorporates strictly the empirical to an OSCM that includes not only the empirical, but also clinical practice and theoretical concepts and models as other pathways for providing evidence (Fuller 2021; Northcott 2022; Nyabadza et al. 2021; Parkkinen et al. 2018). Finally, our proposed OSCM involves not just focal mechanistic models, which usually neglect contextual conditions, but also systemic conceptions of pathological functions, including respiratory dysfunction, hyperinflammation, and so on (Tretter et al. 2021; Tretter et al. 2022).

2. Evidence-Based Corona Medicine

EBCM's chief goals have been to treat safely and effectively the respiratory diseases, as well as nonrespiratory diseases, associated with the Covid-19 pandemic, and to vaccinate the public against Covid-19. Although the pandemic has reinforced those goals, it has also challenged them (Rao 2021; Rehman et al. 2021). Initially, the goal of treating Covid-19 patients involved repurposing pharmaceutical drugs. Specifically, the pharmaceutical industry turned to known antiviral, antimicrobial, antiparasitic, and even anticancer drugs in an effort to treat the viral infection (El Bairi et al. 2020; Guy et al. 2020). However, preliminary outcomes were not entirely successful or conclusive (Kotecha et al. 2020; Martinez 2021). For example, in a randomized, double-blind, placebo-controlled study, ivermectin, an antiparasitic drug, did not significantly prevent hospitalization of Covid-19 patients (Vallejos et al. 2021).

Besides the challenge of repurposing drugs, another major challenge facing EBCM is the time it takes to conduct a randomized controlled trial in order to determine an innovative drug's safety and efficacy. The timeline for development of such a drug averages a little over eight years (Brown et al. 2021). Obviously, such a timeline is a challenge for EBCM, especially in terms of using it clinically. As Trisha Greenhalgh articulates the challenge facing EBM vis-à-vis Covid-19, "where multiple factors are interacting in dynamic and unpredictable ways, naturalistic methods and rapid-cycle evaluation are the preferred study design" (Greenhalgh 2020, 2)—which, of course, is counter to EBM's methodological philosophy. In other words, EBM generally depends upon slow science, rather than fast science (Simon 2021). Moreover, as Marjolein Moleman and colleagues articulate the challenge, formulating EBM guidelines for clinical practice in the corona age does not necessarily require "getting things right" in terms of randomized controlled trials or metanalyses but rather "getting things right *now*" with respect to less rigorous studies and observations (Moleman et al. 2022, 49; emphasis added).

Besides drug repurposing and development, coronavirus vaccines were advanced as the other major goal of EBCM. Their development has been celebrated as its greatest success, even though several challenges emerged with conducting clinical trials to guarantee the safety and efficacy of the vaccines (Kim, Marks, and Clemens 2021; Tregoning et al. 2021). In addition, psychological and social challenges have emerged, especially with regard to those who are hesitant about vaccines (Machingaidze and Wiysonge 2021; Sallam 2021). Many people have concerns about the vaccines' safety. Although part of the biomedical community's response to that emotional reaction is to foster altruism and hope in the vaccine hesitant for the vaccines, the results have been diverse (Bendau et al. 2021; Chou and Budenz 2020). Besides the vaccine hesitant, vaccine refusers or "antivaxxers" are alleged to represent a challenge to achieving herd immunity (Ahmed 2021; Ashton 2021). Unfortunately, the major challenge has been one of (mis)communication (Mercuri and Gafni 2022; Olliaro, Torreele, and Vaillant 2021). Although the vaccine hesitant and resistant have been a challenge for EBCM, they need to be included in the discussion with other stakeholders over the role of vaccines in confronting the coronavirus pandemic (Boodoosingh, Olatunde, and Amosa-Lei Sam 2020; Kärki 2022).

Although much of the political action and many of the governmental policies concerning vaccines have had a positive impact on responding to the Covid-19 pandemic, the challenges emerging with regard to vaccines have had a detrimental impact on the response to the pandemic. For example, in the United States, the public's reaction to government policies enacted to contain the pandemic with respect to vaccines has resulted in a polarization of the different states based upon political ideologies and parties (Clark 2021; Guess et al. 2022). Specifically, in the United States, political conservatives are less credulous about the scientific rhetoric that vaccines are safe or even effective, which has resulted in what is called "red Covid" (Leonhardt 2021). The issue has become one of distrust not only of government but also of science (Cairney and Wellstead 2021). Moreover, distrust of the scientific evidence is exacerbated by an "imperfect science" associated with EBCM, which has at times crippled governmental responses to the pandemic (Mandavilli 2022). Fundamentally, the challenge is what constitutes reliable evidence for formulating government policies that the public trusts and acts in accordance with, especially in a culture dominated by mass media and social media (Li, Pastukhova, et al. 2022). Moreover, another challenge is the well-known discrepancy between public health measures that were implemented or stopped according to the variations of incidence numbers—there were only the numbers used for the public, but no factual explanation, for instance by mechanistic models of the pathology, was provided (Tretter and Franz-Balsen 2020). This is partially due to a lack of a consensus scientific theory of the pandemic as well as the proliferation of conspiracy theories (Douglas 2021; Pummerer et al. 2022).

At the root of the challenges facing EBCM are several implicit assumptions. The most fundamental assumption is reductionism; that is, the whole *is* the sum of its parts (Beckmann and Lew 2016; Upshur 2005). The EBM and biomedical communities accept and promote reductionism for several reasons, including the simplification of complex biological processes to identify and analyze their mechanisms. Reductionists assume robust causal relationships between higher-level processes and their component parts. In other words, lower-level entities and their properties are assumed to be causally sufficient in producing higher-level entities and their properties. Thus, reductive analysis and synthesis are implicitly assumed by EBCM advocates to be adequate for investigating and explaining complex biological phenomena, especially from a statistical perspective, including pathological phenomena such as Covid-19. But reductionism has faced criticism, especially in terms of oversimplifying complex processes and confounding causes and effects (Beresford 2010; De Simone 2006).

The other major implicit assumption for EBM is linear dynamics and causal mechanisms (Marcum 2020b; Sturmberg 2019). Linear dynamical systems are often rather straightforward in their operations and are generally modeled or simulated to provide outcomes that are predictable in terms of both determinacy and certainty (Thyagarajan and Kalpana 2021). Specifically, these systems usually assume that linear dynamics are constituted by negative and positive feedback and feedforward loops, such that one agent causes deterministically an outcome that feeds back, for example, onto its causal pathway. At its core, a system's linear dynamics includes both the structure or sequence of its mechanism and its function, especially in terms of its outcome vis-à-vis its input. For many, if not most, linear causal mechanisms, the outcome is proportional to or depends directly on preceding events, and a simple mathematical relationship or formula predicts and determines the outcome. And linear causal dynamics is thought to be sufficient to account for disease etiology (Marcum 2020b). Indeed, disease is viewed as a disruption in the linear mechanisms and dynamics constituting a particular function.

In contrast to EBM's implicit philosophical assumption of linear causation, most diseases and illnesses, as discussed in the next section, are explained through complex nonlinear dynamics and causal mechanisms, especially Covid-19 (Harvard and Winsberg 2021; Greenhalgh et al. 2022; Sturmberg 2019). Consequently, EBM alone has been unable to provide the necessary healthcare to address the pandemic effectively and efficiently. Indeed, Greenhalgh and colleagues propose the inclusion of causality evidence, methodological pluralism, and systems thinking into EBM to address the Covid-19 pandemic because of problems associated with the applicability of EBM's evidence hierarchies to the rapidly changing nature of the pandemic clinically. "It is time," they conclude, "to bring in a wider range of evidence and a more pluralist approach to defining what counts as 'high-quality' evidence" (Greenhalgh et al. 2022, 253). We agree, another path must be taken—to which we now turn.

3. Organismic Systems Corona Medicine

To address the challenges facing EBCM, especially with regard to overly reduced or simplified focal models, we propose to extend EBCM to an OSCM based on Bertalanffy's organismic biology and systems theory (Bertalanffy 1968; Tretter 2019). Importantly, Bertalanffy theorized that the organism is a system not simply composed of its biomolecular components, but it also exhibits behavior embedded in an environmental or ecological context. He understood living systems as structured wholes that perform at dynamic equilibriums through state-enhancing and state-attenuating loops. A contemporary of Bertalanffy's, James Miller (1973), also constructed a multilevel conceptual framework for the human being as a living system that performs specific functions critical to its existence and development. The classic approach of both Bertalanffy and Miller to systems biology has immense implications for advancing EBCM and patient and public healthcare in the corona age since the proposed OSCM envisages the pandemic as a result of individuals with their personal vulnerability, as well as their collective public agency.

OSCM also advances, besides EBCM, both George Engel's biopsychosocial model (Engel 1980) and Leroy Hood's P4 systems medicine, which incorporates omics technology in treating the individual patient, so that healthcare is predictive, preventive, personalized, and participatory (Hood 2013). Indeed, healthcare, according to the proposed OSCM, is an outcome of the integration of biological, psychological, social, and ecological factors. With regard to health and disease, the disciplinary structure of academic medicine might be used as a taxonomic template not only to conserve diversity, but also to achieve greater unity in it. Besides the natural sciences, such as physics, chemistry, and biology, along with anatomy and physiology, and pathology, radiology, clinical chemistry, and pharmacology, clinical phenomena can be understood by using biostatistics, psychology, and sociology, as well as epidemiology and other disciplines that support clinical work (Tretter and Löffler-Stastka 2019). Currently, these medical disciplines suffer from disintegrated myopia, and they would benefit from a systemic conception of the human organism. Although the proposed OSCM shares with postgenomic P4 systems medicine's reliance on various omics associated with systems biology, such as genomics, epigenomics, and transcriptomics, it also includes other omics and their associated systems science, such as connectomics and systems neuroscience, psychomics and systems psychiatry, health economics and health systems economics, enviromics and systems ecology, exposomics and systems epidemiology, and viromics and systems virology (Table 1).

Table 1. The omics and systems sciences of the factors associated with health.

Factors	Omics	Systems sciences
Biological	Genomics/Epigenomics Transcriptomics/Proteomics Metabolomics/Nutrigenomics Physiomics Pathomics Immunomics Vaccinomics	Systems genetics Systems cell biology Systems nutrition Systems physiology Systems pathology Systems immunology Systems vaccinology
Psychological	Connectomics Cognomics Psychomics	Systems neuroscience Systems psychology Systems psychiatry
Social	Health economics Urbanomics Infectomics	Health systems economics Political systems science Systems infectiology
Ecological	Enviromics Exposomics Toxomics Microbiomics Viromics	Systems ecology Systems epidemiology Systems toxicology Systems microbiology Systems virology

The proposed OSCM focuses not simply on personal health but also—and more so—on public health. In contrast to P4 or molecular systems medicine or biology (Hood 2013; Tretter and Löffler-Stastka 2019), organismic systems medicine, as noted above, integrates biological, psychological, social, and ecological factors, with respect to personal health (Figure 1). Although it is comparable to Engel's biopsychosocial model, in terms of the biological, psychological, and social factors of health, the proposed organismic systems medicine updates and expands Engel's model in that it includes the postgenomic omics revolution in the biomedical sciences. As depicted in Table 1, personal and public health are the result of various omics and associated systems sciences. Finally, the proposed model differs from Engel's model in that it includes and stresses the importance of public health, which emphasizes and distinguishes between social and ecological factors. And, in contrast to the biopsychosocial model, the proposed organismic systems medicine includes ecological factors as crucial for maintaining both personal and public health in that health reflects the state of environmental, ecological, and planetary health (Friis 2018; Horton and Lo 2015).

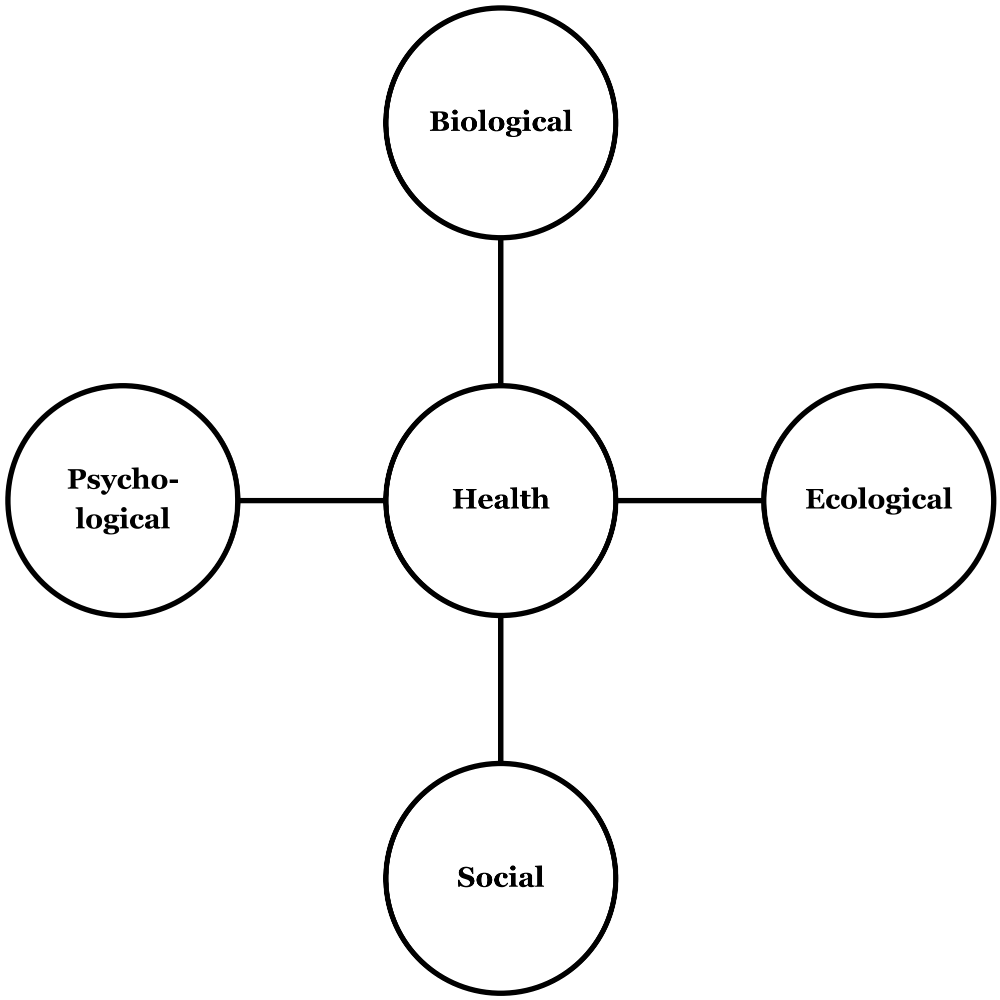

Figure 1. Health is the product of integrating biological, psychological, social, and ecological factors.

Although the proposed OSCM does share with P4 systems medicine an emphasis on prediction of possible health problems based on biological factors, it differs in that it also incorporates into the prediction calculus psychological, social, and ecological factors, which can have an impact on forecasting health problems not only for an individual, but also for the public and the planet. Moreover, it acknowledges the relevance of uncertainty, whether stemming from variability within a system, or our limited knowledge of it (Van Asselt and Rotmans 2002). OSCM—in contrast to EBCM, the biopsychosocial model, or P4 medicine—does not assume that uncertainty compromises our ability to make predictions, given the complexity of living systems. Specifically, organismic systems medicine incorporates uncertainty into its understanding of health and does not eliminate it, as EBM is claimed to do (Tyagi et al. 2015). Rather, uncertainty functions as a constraint for understanding personal, public, and planetary health. In other words, uncertainly concerning the precise impact of the biological, psychological, social, and ecological factors upon health must be acknowledged and included in the prediction calculus in order to maximize efforts to prevent disease and to promote health. For example, although the impact of behavioral changes like mask-wearing were not justified evidentially at the pandemic's beginning, such changes are warranted from an organismic systems medicine perspective in terms of reasonable precautions (Greenhalgh et al. 2020; Tretter and Franz-Balsen 2020).

Moreover, the proposed OSCM is not simply concerned with the prediction calculus of possible health problems or disease states resulting from the Covid-19 pandemic, but also with how best to maximize or optimize health. Consequently, OSCM engages in promoting health, rather than simply predicting and thereby preventing infection or disease. This distinction represents a crucial difference from EBCM, which defines health in terms of SARS-CoV-2 infection, and even from the biomedical model and P4 systems medicine. Rather than limiting health to a default mode, health now becomes the guiding or driving value for medicine and healthcare. Of course, how to define health, whether personal or public, represents a particularly important philosophical task for theoretical medicine like OSCM. Unfortunately, health has been a traditionally difficult and problematic concept to define.

Although no consensus definition for health currently exists, the 1948 definition of the World Health Organization (WHO) is commonly cited within the literature. "Health," according to WHO, "is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO Interim Commission 1948, 100). Although WHO's definition has faced criticism since its inception, especially concerning the possible attainment of "complete" well-being, more recent criticism focuses on the current increase in chronic diseases and disabilities (Huber et al. 2011). In other words, people with chronic diseases and disabilities are not necessarily unhealthy. The current focus is on capability and positive health: "Positive health focusses on someone's capability rather than incapability, which means that people with chronic diseases or disabilities are no longer automatically seen as 'not healthy'" (Van Druten et al. 2022, 2). Recently, Fabio Leonardi has captured the practical dimensions of health qua capability by defining health "as the capability to cope with and to manage one's own malaise and well-being conditions" (2018, 742). Health from such a capability approach involves the ability to make apt choices for realizing one's capabilities functionally.

We propose a definition of health based on our organismic systems approach, as well as upon the capability approach to health. To that end, we expand a person's physical, mental, and public dimensions of health to include planetary health, which is defined as "the achievement of the highest attainable standard of health, wellbeing, and equity worldwide through judicious attention to the human systems—political, economic, and social—that shape the future of humanity and the Earth's natural systems that define the safe environmental limits within which humanity can flourish" (Whitmee et al. 2015, 1978).

We define health as a person's or population's agency to function physically/biologically, psychologically, socially, and ecologically, in terms of abilities, capacities, and expectations based on well-defined values and preferences within a public and planetary context (Figure 1). In sum, a comprehensive definition of health must include not just the personal, but also the public and the planetary. We believe our definition is comprehensive and captures personal, public, and planetary health in a robust fashion. In other words, our definition of health is transdisciplinary since it contravenes disciplinary boundaries to transform our understanding of health with respect to the person, the public, and the planet. The challenge facing what we have proposed is how best to operationalize the definition, especially in terms of measuring health (Huber et al. 2011; McDowell 2006).

In contrast to EBCM's assumptions of reductionism and linear dynamics, the chief assumptions for the proposed OSCM are holism and nonlinear dynamics (Marcum 2020b; Tretter 2019). The assumption of holism relies on the notion of wholeness, which entails an irreducible and a dynamical totality that is complete and undivided (Berlin, Gruen, and Best 2017). The main idea behind the assumption is that the investigation and explanation of natural phenomena or systems and their properties only in terms of their component parts and properties is insufficient; rather, the whole must be investigated and explained on its own terms. Traditionally, the whole is defined as greater, different, or other than the sum of its parts (Heider 1977; Shealy 1979). The proposed OSCM comprehends the impact of the pandemic not simply from its parts, whether biological, psychological, social, or ecological, but also from how those parts interact with respect to systematic principles and rules.

The other important assumption is nonlinear dynamics, which is related to holism and refers to a system and its properties that are not directly or linearly relational or proportional to the summation of its parts and their properties. Rather, complex systems, as noted above, often exhibit nonlinear dynamics in which the outcome of the system's function is nonadditive or synergistic, rather than additive (Tranquillo 2019). Synergistic interactions among the system's components is critical for the emergence or appearance of its functional capacities or agency (Corning 2014). Moreover, most diseases can be represented through "cybernetically-steered, closed-loop models" (Musalek 2013, 172). Thus, the proposed OSCM operates from a holistic perspective, particularly from diverse levels reflecting biological, psychological, social, and ecological factors. And these factors interact synergistically both within and across the various levels in terms of nonlinear dynamics to provide an effective and efficient response to a pandemic like Covid-19 with respect to personal, public, and planetary health.

4. Conclusion

Given the challenges facing EBCM during the Covid-19 pandemic, particularly with respect to randomized controlled trials, we propose an OSCM to address those challenges by integrating the pathophysiological, psychological, social, and ecological dimensions of health at personal, public, and planetary levels. Specifically, OSCM integrates (1) biological factors such as genomics, epigenomics, and proteomics, along with the physiomics, immunomics, and pathomics, to provide a cohesive and comprehensive picture of the individual and/or typical patient qua person, rather than a fragmented and partial picture (Li, Gao, et al. 2022; Tretter et al. 2021). It also incorporates (2) psychological factors into that picture, which can attend not only to the challenges of behavioral disorders like depression resulting from lockdowns, but also to existential fears associated with vaccine hesitancy. Moreover, the multilevel perspective of OSCM addresses (3) social challenges—particularly the political dysfunction that has exacerbated the pandemic—through providing the resources for communicating sound information for both participation at the individual level and at the public or global level (Ball 2021). Lastly, it confronts (4) ecological challenges connected to the pandemic, especially in terms of enviromics and exposomics. For example, Covid-19 is a zoonotic disease and is thought to have originated from wild animal markets in China (Wong et al. 2020). The lesson here is that we must regulate our invasion and exploitation of habitats that might contain viruses, which can cause pandemics (Marcum 2020a).

Finally, the proposed OSCM addresses the challenge of what Ed Yong (2020) calls the downward "pandemic spiral." Yong claims that the attempt in the United States to remedy the pandemic has been to enact one response after another in a linear fashion, rather than in concert with one another. We contend that OSCM would resolve this challenge by integrating the numerous factors that comprise the pandemic, including biological, psychological, social, and ecological factors. Moreover, it would help to develop a robust storyline for articulating not just what the pandemic is but, more importantly, how to respond effectively and efficiently, both individually and collectively. A major challenge to EBCM's response to the pandemic has been not only the quality of the evidence, but also how best to interpret it for narrating a storyline to respond effectively and efficiently (Pfaff and Schmitt 2021; Sturmberg et al. 2021). The proposed OSCM provides a novel starting point for developing the theoretical framework needed for narrating a robust storyline through integrating the numerous factors involved in the pandemic's complexity and hopefully avoiding the bottom of the downward spirals for future pandemics and other potential public health crises.

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