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Review article

Bioresilience 2.0: reconsidering preparedness and response adaptability against high uncertainty in surging and repeated bioevents

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Abstract

Suboptimal management, declining host immunity and fitness, and increased pathogen diversity, evolution, and emergence constitute, as a whole, a worrisome biosecurity perspective, especially through the One Health lens. This article aims to increase systemic resilience, robustness, and effectiveness against bioevents affecting the entirety of potential hosts, including humans, animals, plants, and microbes, in all relevant environments: urban, rural, industrial, hospital, and wildlife. Bioresilience 2.0 integrates better governance with improved cognition and diverse relevant technologies to make preparedness and response relevant, adequate, sustainable, and affordable. The main message of this conceptual review is that emerging bioscience technologies, empowered by new or improved concepts and operating procedures, implemented through hardware derived from other fields, and governed optimally, may result in more effective preparedness and response. As practical implications, less systemic liability and increased readiness are expected, with dispersed, multiple, sustainable formats achievable through affordable commercial support technologies and means, coupled to integrative approaches that stress flexibility, procedural and technical synergies, and are informed by integrative thinking across sectors and by innovative, coordinated planning by the respective implicated agencies, which would guide surveillance and intervention.

Keywords: Bioresilience, Biosurveillance, Decontamination, Global Catastrophic Biological Risks, Host species barrier, Microbiome, One Health, Zoonoses

Introduction

The Humanome, a term encompassing the entirety of human subjects plus any biological or non-biological entities directly dependent on them for survival, sustenance, and/or maintenance [1], has always been severely impacted by the microbiota [2, 3]. It seems that, in the foreseeable future, this will not change.

The notion that infectious diseases might be eradicated proved a fallacy [4]; only two diseases, both of viral origin, have ever been eradicated: Smallpox in humans since the 1980s [3, 5] and the zoonosis Rinderpest since the mid-2010s [6]. The advent of the concept of the microbiome [7] also advised against such a prospect, as it proposed that microbiota are present on all hosts, fomites, habitats, and niches and are associated through a complex network of interactions, exchange of genetic information [8], and the transit of actual populations. This issue is especially relevant to human health regarding zoonotic agents, which frequently cross host species barriers [9, 10].

The One Health concept originally focused on the vulnerabilities of affluent, well-funded, and developed Public Health systems to epidemics transmitted from diverse, less surveyed environments (rural, wildlife, industrial) and from remote, Public Health-challenged polities, due to the extensively globalized international environment. It expanded, however, to include non-human hosts such as animals, plants, and microbes. In both iterations, it has been predicting increased impact of infectious diseases, not mitigation of their occurrence; much less eradication [11].

A concept of the 90s, the 'Black Biology' may be understood as the illicit practice of biodisciplines, especially microbiology, in unlicensed facilities, irrespective of the sophistication of the practice and equipment. It remains a risk area for accidental, but mostly malevolent release of pathogens. Different spinoffs, especially in a bioterrorism context [12], may create more threatening bioagents by exploiting diverse, affordable conceptual and technical advances. These include genomic engineering, organism engineering, functional genomics, various sectors of microbiomics, and iterations of bioinformatics, including Artificial Intelligence [2, 13, 14].

Moreover, the development of legitimate biotechnology, especially within the framework of the bioeconomy, suggests risks of major, industrial-scale accidents and massive disruptive impacts. Such prospects

have resurrected concerns about the possibility or probability of global-scale events, from Global Catastrophic Biological Risks (GCBR) [15] causing GCBE-Global Catastrophic BioEvents, to existential risks and threats, causing Extinction-Level Events (ELE) [13]. COVID-19 would be the archetypal GCBE, but it was instead characterized as a Public Health Emergency of International Concern (PHEIC) [16]; a much less alarming description.

Consequently, the global Pan-microbiome (understood as the sum of local microbiomes of any kind, retaining their particular structural, qualitative, and spatial characteristics, not merely the sum of microbial taxa) is likely to transform. Initially, qualitatively, numerous novel species may emerge rapidly, as did *Candida auris* [17], and subsequently, higher taxa may follow suit. At a later stage, current microbiomes might shift as the emerging microbiota could occupy existing niches and habitats and carve new ones. A quantitative transformation is also plausible, as entirely novel microbiomes may emerge. The concept of Infectomics [18] was considered a perceptive tool for handling the uncertainties introduced above. Its cognitive extension to the Pan-infectome (understood as all potentially infectious entities within the Biosphere, irrespective of location or host) is proposed herein to accommodate multiple host populations and the transitions among them, as perceived by the One Health concept.

In this setting, the notion of Bioresilience 2.0 (B-R 2.0) might be helpful in mitigating prospective biorisks targeting human, animal, plant, and microbial hosts, present in hospital, urban, rural/agrarian, industrial, or wildlife environments (Table 1), including the prospect of transmission from one host or environment to some or all of the others, as suggested by One Health. The B-R 2.0 conceptually integrates lessons learned after the COVID-19 pandemic with previous Bioresilience iterations [19].

Table 1: Impact and risk of trans-sectoral transmission by environment type.

Environments	Humans	Animals	Plants	Microbiota
Industrial	M	M	H	H
Medical	H	L	L	H
Urban	H	H	M	M
Rural	M	H	H	M
Wildlife	L	L	L	H

A combination of factors, mainly the prevention/response measures, physical distance, biological intrapopulation diversity, and the qualitative and quantitative characteristics of interfaces and interactions, defines the impact and risk of disease transmission among different host types in diverse bio-habited environments. L = Low; M = Medium; H = High (refer to impact & risk).

The most important novelty is the need to prepare for massive disruptive effects that can occur even in sectors and locations seemingly unaffected by the pathogen itself. Such disruptive effects, like shortages (even temporary ones) of medicaments and diagnostics, plus the quarantines and lockdowns that disrupt transportation and the relocation of assets, must be taken into account during planning. Specifically, mitigating their detrimental effects must be considered a prerequisite for proper, effects-oriented governance in the field of preparedness.

From the above, it follows that B-R 2.0 is much more expansive in application than biosecurity and its sensory arm, biosurveillance. This is because it also delves into assets and processes that are only indirectly implicated but remain vital for response and mitigation of detrimental effects. It addresses a much wider, multi-sectoral set of liabilities than Health-system Resilience and One Health preparedness, as it includes diverse assets beyond the biomedical sector, even if the latter is taken *sensu lato*. Last, but not least, it relates mainly to spontaneous, natural occurrences, in contrast to the Disruptive Biosecurity concept, which is highly intrusive and conceived as reactive to perpetrated biothreats [20].

The methods

This is a conceptual review drawing on literature relevant to One Health, biosecurity, GCBR, decentralized diagnostics, environmental and genomic surveillance, microbiomics, synthetic biology governance, and emergency logistics. It focuses on scientific speculation based on scientifically proven facts and on projecting their impact for strategic oversight. It is a top-down synthesis, with a central idea/concept introduced and then supported or discredited by references selected to validate the idea, rather than collecting all relevant literature and then extracting the relevant/supportive ones, an approach discouraged by the limit on reference count, no less.

Although the responsible reporting and communication precautions have no particular merit once Gain-of-Function (GoF) studies began being performed and published in the early 2000s [21] and continue to be so [22], this work contains no actionable or unpublished sensitive information that cannot be freely retrieved by unauthorized individuals. The issue of “dual-use”, being highly subjective, is treated arbitrarily.

The problem: the three aspects of biorisk amplification

The danger of ELE caused by infectious agents is real and present [13], and to a substantial extent this is due to suboptimal infection control strategies and methods, a fact amply demonstrated in the management of COVID-19 [23]. The failure to contain diseases overall is due to three broad reasons, as detailed below.

Devolution of target populations

Devolution, in this context, is understood as the reversal of outcomes expected by Natural Selection. It emerges

when Natural Selection is nullified or reversed, and refers to lower innate immunity, higher susceptibility to pathogens, and vulnerability to the cascade of effects an infection may cause. Natural Selection is made redundant not only among humans but also among other species, especially those that are highly dependent on humans and just as important (breeds, cultures), which also happen to interface most with them.

Directed genomic modification is not widespread in humans at this time. However, it is far more common in species that are extensively cultivated or bred for a range of economic and financial reasons. These extend from pets and ornamental plants [24] to industrial processing, as in surface biomining of low-yield or exhausted mines [25], and to the food and beverage industry and the feed industry for companion and productive animals [26], as well as to biofertilizers/biostimulants for plantations of any size [27]. Such genetic improvement may not necessarily be through genetic engineering. Selective mating and cross-pollination result in the same common denominator: new lineages with maximized desired qualities [28], at the expense of fitness, especially regarding resistance to and resilience against infection. This constitutes the preponderance of Artificial Selection over Natural Selection [29]. The administration of protective and therapeutic regimens and the creation of protective environments, such as repeated disinfection of surfaces and objects during COVID-19, compensate for lack of resilience and immunodeficiency. Thus, instead of robust, resilient, and fit individuals and populations, production efficiency (by whatever standards) has been prioritized for centuries. More or less sustainable, higher- or lower-end technology shields all individuals, allowing an unprecedented expansion of the humanome [30] but destabilizing its balance with surrounding multi-microbiomes. Such external protection selects for more robust pathogens and further degrades any levels and motivations for Natural Selection to intervene in matters promoting immunity and resilience. Coupled with decreasing immune efficiency, this last factor results in the population's fitness devolution [31].

Furthermore, the extremely dense conditions in breeding farms and in massive cultivations facilitate contagion. Moreover, the genetic homogeneity, especially within the latter due to the clonal nature of the plants, but also, to some degree, within the former due to pedigree selection, suggests that once a disease occurs, compromised immunity makes this more likely to happen sooner rather than later [32]; the impact will be catastrophic and the spread immediate. No genetic diversity is left to introduce barriers, with the Irish famine due to potato blight being the paradigm [33]. Massive transportation and travel can spread the disease globally within a few days. If this happens within the incubation period of the pathogen, multiple outbreaks would occur once symptoms develop [34].

Accelerated pathogen emergence and adaptation

The rapid development of antimicrobial resistance (AMR) and its broad dissemination within a single generation through mobile DNA elements among mixed but collocated microbial populations undermine antimicrobial interventions by chemical and biochemical means, largely by accelerating the obsolescence of antibiotics and other antimicrobials [35].

The long-standing deterioration of immunity and AMR dimensions is currently and prospectively perplexed by an expanded pathogen base [36] due to the emergence of the Neopathogens, new pathogens in ecological and geographical terms stemming from existing species. The first case refers to the breaching of the host-species barrier [37] and to existing commensal species becoming opportunistic pathogens due to deterioration of immunity. The second case refers to pathogens migrating to new locations and hitherto benign host populations due to transportation and travel [15]. Metapathogens, on the other hand, result from modification, a case of anthropogenic breaching of evolutionary limitations [2, 15, 21]. Neo- and Metapathogens drastically expand the Pan-infectome in planetary terms.

A newly appreciated class of transmissible diseases, namely cancer, is likely to further diversify the Pan-infectome. Metastasis is a transmission among different biocompartments and thus microenvironments, implemented within the physiological and spatial constraints of an individual, irrespective of its taxonomic status. Iatrogenic or other conspecific transmission through allogenic blood transfusion [38] or solid organ transplantation [39] is possible, despite the scarcity of evidence. The low occurrence observed [38, 39] is a biased conclusion, due to the stringent testing and mitigation measures intended to exclude such events. It is possible in a conspecific context, although not probable. But probability is not the issue; possibility is. There is one more contagion mechanism and sector to take into consideration for Bioresilience and Public Health.

As internalization seems required for cancer contagion, the possibility is low, but host jumps, as a principle, are disquieting. Close contact, third-species vectoring, carriage by fomites, or even environmental transmission may be conditionally possible: Transmissible cancer events in conspecific settings have been observed in dogs, Tasmanian devils, and catfish [40], and the transmission mechanism remains elusive. If it evolves to the point of crossing host species barriers, interspecific transmission might occur. In this scenario, the dogs would pose a major Public Health risk and potentially a biosecurity one as well. So would marine lifeforms, becoming exemplary One Health concept biorisks, possibly disseminating cancer

through the hydrosphere to diverse species via some transmission mechanism(s). Such host species jump mechanisms might already have evolved, but if so, they remain unobserved.

The combination of a wider Pan-infectome with ample substrates, permissive conditions for transmittance (inter- and intraspecifically), and intense selective pressure caused by overuse, if not abuse, of antibiotics and other antimicrobials is likely to result in prompt pathogen evolution and an accelerated rate of emergence of very aggressive, fit, resistant, and transmittable pathogens, dubbed the 'microbial apocalypse' [41]. Their AMR level ranges from multidrug-resistant (MDR), through extensively drug-resistant (XDR), to pandrug-resistant (PDR) agents. Thus, the definition of super-pathogens, which has been "pathogens displaying resistance to multiple classes of antibiotics" with an emphasis on bacteria [42], may shift to "pathogens incorporating, by engineering or by natural recombination events, virulence factors that neutralize immune response, perplex medical treatment, or both". The expanded definition accommodates microbiota other than bacteria, not concerned with nor susceptible to antibiotics (*sensu stricto*), such as viruses; but also provides for other forms of survivability, functioning against antimicrobial factors other than drugs. A characteristic example is engineered viruses with GoF treatment to enable them to derail immune responses [21].

Accidents (spontaneous or deliberate) in biotechnological facilities may release unknown, experimental, or patented microorganisms, possibly pathogenic (Metapathogens) or biocompatible and facilitating pathogen transmissibility. The escaping microbiota, if custom-engineered for research or productive purposes, might prove unidentifiable and subject to further evolution, adaptation, or modification.

Infectious agents may breach host-species barriers. Examples abound: zoonotic or benign animal viruses can shift host populations, as with HIV and SARS-CoV-2 [36, 43], through a series of probabilistic postulates. The main such postulates are, first, some similarity in receptor moieties; second, the susceptibility of the respective cells to the particular viral infectious mechanism; and finally, the actual event of transition from the original to the novel host environment. Adaptation is passive, and actual agent evolution is irrelevant. The simpler the agent, the higher the probability of compatibility with alternative hosts and, potentially, with hosts of extremely different phylogeny [44].

Alternatively, the ability to breach the host-species barrier may arise through evolutionary steps in a deterministic manner, as is typical of more evolved and complex pathogens, such as fungi [45]. An organism with more elaborate adaptive mechanisms may undergo actual evolution to secure additional or alternative hosts, preferentially refining its most relevant mechanisms, such as a wider assortment of digestive enzymes and diverse dispersal strategies, rather than mechanisms advancing other skillsets, such as biomarker-based selectivity [46].

Suboptimal management of assets

This category includes shortages in the development and supply of appropriate and efficient therapeutics and diagnostics [47], including the high cost for large population groups. Along with reasons directly or indirectly related to drugs, key factors also include the globally deteriorating public health standard [48] and the rapid expansion of immunocompromization [49], iatrogenic and spontaneous (idiopathic or not). Thus, possible hosts become more susceptible to infection, producing larger infected and diseased populations. This increase drives up the frequency of dissemination and the onset of epidemics or pandemics; it also allows a much wider host basis for faster incubation of evolved strains [50], and, last but much more important, increases the number of prospective requesters of medical attention, including but not limited to treatment.

The bottleneck in antimicrobial drug development, an event recurring across different antibiotics, is a long-standing liability, despite occasional breakthroughs, such as the advent of the echinocandin antifungals [51]. There are many causes, the most important being the rapid development and prompt dissemination of resistance-AMR [52]. Consequently, antibiotic stewardship is a measure occasionally implemented with utmost severity, though not uniformly [47]. But AMR is not the only cause, and it is usually overstated. On the contrary, irrationalities in the drug development pipeline, from initial conception to routine use and then obsolescence [47], are commonly ignored, despite their importance and possible implications in the emergence and massive propagation of dissemination pathways amongst microbiota.

The One Health interfaces of the threat

To a considerable extent, the gravest issue in systemic terms is internal and thus amendable. It is a matter of priorities at the levels of Policy and Grand Strategy. There are serious external problems and bottlenecks, as well as the nature of perpetrators and bioagents. But resolving internal, systemic frictions and incompatibilities would greatly assist the effort. For example, optimizing resource use and rational planning [36] should be preferred to a mostly obsessive pursuit of profitability, based on optimization and competition.

Pathogens disrupt biological and ecological balance and economic activity as they move back and forth among different host species that may belong to different Kingdoms of Life and inhabit diverse environments. Thus, they may accumulate evolutionary traits, including

resistance to antimicrobials. Consequently, coordination and cooperation among all involved agencies, from different health upkeep services (public, environmental, and agronomic) to security ones, is a prerequisite. Not for optimizing preparedness and response, which is a valid but distant goal, but merely for achieving basic functionality and relevance in these fields. Such concerns define the Bioresilience 2.0 approach, as will be detailed below.

The breach of the trans-sectorial host-species barrier is conditional on the implicated agents and the source and target hosts by sector (Table 2). This conditionality is exemplified by paradigmatic plant pathogens, such as the fungal genera *Fusarium* and *Aspergillus*, which are facultative but occasionally lethal human pathogens [53], and *Claviceps purpurea*, which poisoned entire communities and their livestock [54]. Thus, plant pathogens may cause both septic and toxic effects in humans and animals; both modes of action rely on ingestion and/or inhalation as points of entry, though to different degrees; ingestion of mycotoxins is highly morbid, whereas fungal cells and spores are more threatening when inhaled [55].

Table 2: Host trans-sectoral transmission of pathogens.

	Humans	**Animals**	**Plants**	**Microbiota**
Humans		V, B	F, B	B
Animals	V, B		F, B	B
Plants	F, B	F, B		B
Microbiota	B	B	B	

The viruses are very common in host-species barrier compromises among animals and between animals and humans. The physiologic diversity of the bacteria makes them much better barrier breakers between Kingdoms. F = Fungi; B = Bacteria; V = Viruses.

On the other hand, animal pathogens that survive and evolve in animal reservoirs regularly have a major impact on humans. HIV and SARS-CoV-2 infections are indicative [36], but zoonoses are even more important [37]. A considerable number of officially characterized bioterrorism bioagents are animal, not human, pathogens: *Bacillus anthracis*, *Burkholderia pseudomallei*, and the equine encephalitis virus are only some of the examples [56]. As spillover of agents from animal epidemics may trigger human ones, new iterations of current Omics are expected under the prefix 'agro-', with agrigenomics or 'agrogenomics' already emerging in prominence [57], to mitigate the danger.

Proposing a new release of (Bio)resilience: the 2.0

The core idea of Bioresilience 2.0 is to expand beyond the functional pair of detection and intervention in standard Bioresilience formats, with each of these two arms including multiple phases [19]. The intended scope is a more expansive and inclusive format, with greater resistance to entropy, applicable especially to spontaneous but also to perpetrated events, whether transmissible or not. A key priority is to anticipate unexpected and unprecedented events, rather than trying to prioritize expectations and dwell on precedent. Another is to define achievable and efficient ways to increase the robustness, relevance, adaptability, suitability, and sustainability of prevention and response, and the systemic tolerance of functions, services, infrastructure, and threatened populations and ecosystems, whether urban, rural/agrarian, or wildlife. Dispersing testing facilities, for example, mitigates facility overload, reduces delays and risks from sample or patient transit, and allows better awareness on the spot. Some loss in performance and higher costs for personnel might be acceptable compromises and investments, respectively.

The B-R 2.0 is a less demanding and reactive complement to the concept of Disruptive Biosecurity [20], which is conceived for proactive and reactive mitigation of perpetrated biothreats. The B-R 2.0 is based on governance as well as on science. It focuses on passive preparedness, a feature likely to attain considerable commonality throughout the threat spectrum, rather than on active intervention, which is plagued by uncertainties although it is prone to minimize health casualties and damage, especially in perpetrated events.

B-R 2.0 treats One Health as a fact that confirms and amplifies its relevance and usefulness, given the need for quantitatively expanded and qualitatively improved preparedness and awareness; a reason for its very inception. It is not particularly concerned with subordinate One Health issues, even core ones, such as animal reservoirs, zoonotic spillover, environmental microbiomes, and wastewater. All these are handled at a more basic level by the respective, individual implicated agencies and have been the focus of previous iterations.

On the contrary, some other issues, such as expanded and dispersed environmental surveillance (meant to tackle the abovementioned core issues), the development and communication of AMR across sectors, and the coordination between medical, veterinary, environmentalist, and security agencies, are considered vital and essential for the applicability and usefulness of the B-R 2.0. They are essential for detecting, tracking, preventing, and responding to biorisks that may be brewing in some cross-sectoral context.

Regarding governance, under the "prevention through regulation" concept, stakeholders might agree that new microbiota can be used only if licensed, much like medications today. A mandatory testing regimen is thus needed to determine inclusion in or exclusion from the "Select Agents Lists" [58] using positive criteria, before licensing their use or distribution. The heading "New microbiota" would be highly inclusive: fully engineered or

modified microorganisms are obvious participants, but emerging ones would be, too. These would mostly be new discoveries in various environments, detected through metagenomics but verified and characterized through Analytical Culturomics, which are expected to definitively reveal the susceptibilities and vulnerabilities of assayed bioagents [59].

A sensitive issue arises with research resources, as always: good biosecurity practice presupposes regulation, and researchers are unwilling to comply (and their sponsors even less so), largely because of the added cost and effort. Perhaps an understanding could be reached that experimental microbiota/strains should be reported until either discarded/incinerated without any stock kept, or proceed to production, whence they would be examined according to criteria for inclusion in or clearance from Select Agents Lists.

Structure-interrogating sensors/detectors could expand their ubiquity by improving performance in point-of-care, hardware-independent assays in expendable formats, such as strip tests. But the focus will be on integrating detectors, samplers, and agnostic identifiers that can detect novel agents and inherently offer multi-agent resolution [58]. They do not have a preconceived panel of signatures with which to compare the acquired signal, but they compile a sample signature to be processed by much more elaborate equipment/agent-calling amenities. The latter may be remotely located and connected, or rather linked, to respective databases. Metagenomics formats in nucleic acid analysis are the most familiar paradigm to follow [19].

The tools for surveillance and response

Enter the drone

Novel combinations of innovative or legacy effectors with modern or even prospective vectors may yield revolutionary rather than evolutionary results, based on synergy rather than addition and aggregation. There is no need for exotic solutions, such as bots that carry cells or other lifeforms for any kind of intervention, like the highly futuristic Biote-bot idea [60]. Nor is there a need for sous-realistic contraptions like technologically enhanced microbiota (Biohybrids) [61] and the Biobots [62], which are products of existing cells recast in artificial multi-cellular formats. For many B-R 2.0 needs, current drone examples suffice.

The need for low-cost, high-volume autonomous delivery assets emerged during COVID-19 and is now met. Massively available and affordable drones mitigate very similar wartime requirements in Russia and Ukraine since 2024, in Iran since 2025, and, to a lesser extent, previously in Syria in the 2010s. The technology is now mature, and where response teams and manned assets (vehicles and aircraft) were previously needed for surveillance and intervention, drones may now be used, drastically reducing risks, costs, and logistics and support footprints.

Regarding response, transport/carrier drones, both air- and ground-borne, may dispatch necessary supplies quickly to multiple locations at low cost and with increased security, addressing both transit risks in isolated or extreme terrain and bio-risks, focusing on human crews acting as vectors and fomites. The drone may act only as a fomite and is easy to thoroughly decontaminate. This approach allows optimal distribution of limited stocks even under restrictive conditions such as lockdowns, with little danger of fomite transmission of a disease when operating in compromised environments, easy disinfection/decontamination, and a relatively affordable replacement whenever mismanaged, unable to disinfect, or lost. But the importance lies in the absence of risk to human crews and the zero possibility of vectoring the infection through animate subjects during multiple entries and exits in contaminated environments.

Biosurveillance/ diagnostics

Such capability may be an effectiveness multiplier for the dispersed surveillance operations mode, which has been proven during COVID-19, meaning the deployment of early warning and affordable Resource-Limited Settings/RLS diagnostics, including but not limited to Rapid Diagnostic Test/RDT formats, such as the diverse kinds of self-tests [63], which seem to be considered the key in future bioevents. Bio-screening would refer to a definite, targeted action to detect, locate, and then identify the reason for an anomaly, i.e., some divergence from the usual/natural horizon of events, the perception of which is the object of biosurveillance. In such contexts, the ability to dispatch, in spatiotemporal relation, techno-mechanical means efficiently and affordably, so as to conduct sampling or even real-time or near-real-time analytical biosurveillance, is crucial [64].

The dispatch of sensor/surveillance assets with their operators is the original format, used during COVID-19 to monitor locations of interest and points of entry and exit, and to provide access to testing for individuals without long transits and -even transient- high-density spatiotemporal coincidence of potential hosts and vectors, which may result in spikes in diagnostic workloads and possibly compromised diagnoses. This approach suggests portable equipment and protocols designed for RLS conditions [65]. Non-amplification-dependent sequencing, exemplified by the Oxford Nanopore® [66], may be the most relevant such capability. Still, portable PCR settings, based on Peltier or convection principles, and even hybrid ones appearing lately [67], have been the mainstream approach. Microfluidics platforms expand the scope of possible tests while offering a drastically simplified operational solution through RDT formats [68],

instead of laborious, competence-demanding protocols, even if the latter are sustainable and affordable [57].

The massive availability of drones pushes the above further. Transport drones could maintain a steady, secure, and safe supply of as-needed/when-needed consumables, from batteries and spares to expendables (biochemicals, plasticware, or other), including the return of samples, specimens, or waste, thereby reducing the environmental and biosafety footprint. Thus, support for dispersed operations becomes affordable and streamlined. The next step would be the unmanned, automated implementation of distributed, though not necessarily dispersed, surveillance by incorporating air (and other) samplers into drones. As drones may be kept in centralized locations and dispatched ad hoc wherever needed to cover significantly distant sectors serially or concomitantly, distributed surveillance needs not be implemented by dispersed elements, thereby reducing costs. This is a step further, but not truly innovative; it predates the massive implementation of dispersed biosurveillance/bioscreening operations by some years [69]. Still, under duress, as during COVID-19, it could not be utilized, with the possible exception of some polities that selected a deeply militarized response to the pandemic [16]. Drones with modular payload capacity and of some size could even be outfitted with automated equipment to fully conduct the tests and return the processed sample or even the initial readout of such analysis [70].

What is revolutionary is the current affordability of such approaches, enabling flexible planning and large-scale implementation, made possible by modified or custom-designed sensor drones [71]. Equipped with minimal air-sampling provisions and microfluidic platforms [68], they may perform the tests immediately, on the move, and return the completed assay for readout, thereby reducing biosafety concerns as well as sample degradation. Real-time readouts are not conceptually challenging [70] and would allow long, continuous patrols for persistent surveillance ~~over time~~ in sensitive sectors.

Reactive intervention

A more direct, active intervention approach targeting pathogens and risk foci could be implemented using drones, both airborne and ground-based, to disinfect or decontaminate equipment, supplies, and objects, as well as surfaces and spaces/volumes. For example, ultrasound and electromagnetic field generators, and other energy-emitting devices likely to be fielded in the near future that produce antimicrobial effects in specific, adjustable settings could be carried as integrated, exchangeable payloads by small and medium ground and airborne platforms to perform non-chemical decontamination [59]. This can now be transferred to drone hosts, as emitting drones are already used in different applications [72].

Suitable amenities in kind and settings (mostly frequency, duration, waveform, and intensity) would be either identified through comparative setups of culturomics, especially electroculturomics, or predicted by future iterations of functional and translational genomics, such as electrogenomics, a concept similar to pharmacogenomics that should predict the hereditary response of a cell to different electrical amenities [73].

Liquids and aerosols that are more sustainable and less destructive, in environmental and technical terms, than the corrosive chemicals used for decontamination as standard, may be developed and deployed. New non-corrosive oxidative agents [74] are an example of such chemicals, but different biological amenities would also be of interest: different viruses, tuned against cellular or acellular bioagents (bacteria, parasites, and fungi are included in the former category and viruses in the latter) [75], may be aerosolized and dispersed with high quantitative and positional accuracy by sprayers or agricultural drones [76]. The same may apply to biochemical amenities, such as bioengineered enzymes or aptamers designed to degrade bioagents, including but not limited to toxins or viral spikes [77], inhibitors of enzymes and receptors, decoy receptors [78], antibodies/antibody fragments [77], antimicrobial peptides [79], and natural antibiotics, modified or not [80].

More unconventional approaches could be tried. One example is heat-dependent inactivation. Thermobaric or fuel-air explosive formulas for explosive decontamination, or purpose-developed incendiaries for heat inactivation by heat spike or combustion, possibly implemented by some reincarnation of the flamethrowers of the mid-20th century are valid options. They would constitute translation of standard decontamination procedures for biocompromised equipment and assets in hospital waste to field applications.

Another approach could be gelative agents sprayed to trap/restrict/contain high concentrations of released pathogens or plug leaks, especially to contain aerosols. The trapped microorganisms may then be neutralized physically, as already mentioned, chemically, or through bioremediation. This could be achieved by insects, bugs, worms, or other live agents set to consume or at least neutralize the pathogens trapped in the gel [81].

The governance aspect: a matter of management

As mentioned above, the suboptimal management of assets is a key liability in Bioresilience and Public Health. Preparedness for major events requires rejecting the efficient and lucrative “just enough” models, which fail anyway: it is impossible to predict accurately what “just enough” will be, so either economic loss or health casualties will occur; which outcome is deemed acceptable today, is obvious to everyone. On the contrary, surge capacity ingrained into the One Health principle, due to

the need for as much commonality as possible among sectors, is the core requirement across all implicated subfields: surveillance, diagnostics, protection, therapeutics, decontamination, palliative support/care, transportation, and strategic reserves [82].

The issue of diversification extends beyond the above concerns. The concept is not very popular because it always incurs additional costs of different kinds, not only monetary: incompatibilities in support specifications, complications in training, planning, and modus operandi, and many other issues plague it. Still, the diversification of therapeutics offers the best odds that at least one therapy would be effective against any new pathogen, or at least would provide a basis for a quick reaction program to fine-tune promising existing amenities. The diversification should include not just different classes of antibiotics; additional antimicrobial compounds, including non-(bio)chemical ones, should be included. After all, "Diversity is Nature's insurance against Catastrophe" [83].

A trickier but equally vital plane of diversity is that of hosts. Although multiracial societies have been in vogue for some decades now, the approach is not applicable to human hosts. Measures to enforce it for the aforementioned purpose would imply acceptance of Extermination-Level Events as inevitable and a focus on the partial survival of some social elements at certain spatiotemporal coordinates. This amounts to acceptance of the extermination of the others (by any applicable definition of the Other), or, taking a step further, it would be a very neat method of population cleansing – by Denial of Care and through natural processes.

But despite such negative ramifications for humans, this approach is applicable to livestock breeding and plant cultivation and is a wise decision in that context: without monoculture, pursued for efficiency (i.e., profit), the Irish Potato Blight might never have been so destructive [33]. More diverse animal breeding is a potential safeguard against various animal "-poxes" and "flus," which seem unending [21, 84]. Agricultural preparedness not only supports, through the One Health principle, the health, survival, and well-being of humans [11] by restricting the transmission of facultative human pathogens from the rural environment to human hosts. Most importantly, it increases food availability and provides food security. In this context, both the rewilding of domesticated species [85] and the de-extinction efforts [86], although prodigious from an ecological standpoint and irreparably interventionist and intrusive, do carry merit in practical terms.

Conclusions and prospects

Despite different approaches and views, the airborne agent remains the most feared biothreat and will continue to be so in accidental, deliberate, and spontaneous bioevents. It is the most difficult to sample and contain; it disseminates quickly and over long distances and affects extremely vital organs upon first contact. All the above factors favor massive disruptive effects [15], in times disproportionate to the actual destructive ones.

The pathogens, taken collectively, are expected to evolve, especially through human agency. In the 21st century, it is rather short-sighted or simplistic to simply augment a microbe's inherent pathogenicity by genetic manipulation, which usually implies the addition of virulence factors or resistance genes, typically carried on plasmids. This approach defines the 2nd generation of bioagents, the best example being specific strains of *Bacillus anthracis* [23]. The most probable horizon of events predicts that once advanced, efficient genomic engineering protocols are fully developed and mastered, the septic constituent of the pathogen will be deemed obsolete as slow and suboptimal compared to a toxic one added by genetic engineering, perhaps by the CRISPR-Cas9 system ('Clustered Regularly Interspaced Short Palindromic Repeats- CRISPR-associated gene-9') [87]. In such a context, the microbe will not be the weapon, but the vector, as is already the case in some natural instances, like toxin-infested fungal spores [88].

This prospect refers to the 3rd generation of bioagents [23], which entered the stage at the turn of the century with an animal virus gaining suppressive function through the addition of host interleukin genes [21]. In the mainstream cases, as may be predicted, a robust, 'optimized' microbe shall produce an allogenic biotoxin or bioregulator upon germination or by other environmental trigger. The combination of toxic effect with modified, decoupled diagnostic biomarkers intended to evade medical countermeasures of any kind (diagnosis, prophylaxis and treatment) is worrisome. The toxicosis' signs and symptoms would be incompatible with the clinical picture of the septic phase of the infection, and diagnostic algorithms would be nullified. The optimum microorganism would be of high expression efficiency, combined with ample genetic space for the insertion of expression complexes (i.e., promoters, enhancers, other regulatory elements, and an optimized coding sequence), and would be "updated" with a highly effective allogenic, most probably eukaryotic, biotoxin [89] or, for more precise and predictable effects, an allogenic bioregulator.

On the other hand, thoroughly engineered bioagents, although within conceptual reach and clearly within the current state of the art, are not easy to acquire or develop. Consequently, the perpetrated biothreat will conditionally appear as dedicated, custom-engineered bioagents, accessible to a restricted group of privileged users, mostly affluent or technologically advanced state- or state-sponsored ones. Alternatively, it may appear as more basic but affordable, ubiquitous bioagents, rudimentarily, if at all, engineered, because of the dissemination of the novel

microbial modification tools. Intentional such events would include fully synthetic viruses [90] and bacteria with fully artificial genomes, possibly totally or partially transplanted ones [19].

Unintentional modification pathways mainly involve laboratory and bio-industrial accidents at large biotechnology facilities [64]. If SARS-CoV-2 resulted from GoF experiments escaping laboratory biosafety barriers [22], the threat posed by such events is evident. Rather than the extreme morbidity of the 1979 Sverdlovsk incident (whether an accident or sabotage), which was spatially focused [91], global transmission creating GCBR-level effects is to be expected [13].

But the real issue is the microbiomic, not the mere microbiologic attributes of the threat agents. In an era of microbiome biotechnology, many concerns, opportunities, and risks arise. Manipulation of appendage or even environmental microbiomes may alter the dynamics and balance within current ones, favoring existing aggressive microbiota or dysregulating functionally benign but facultative pathogenic microbiota, driving them to full pathogenicity. This can be achieved by environmental factors. An advanced alternative would be to transform benign or harmless agents into aggressive and pathogenic strains and species by releasing recombination factors into their environment, thereby producing infectious potential without ever releasing infectious agents proper. Such factors would be phages, natural or engineered, intended for transduction, or naked DNA/eDNA (environmental DNA) for transformation.

In between lies the microbiomic, not the microbiologic, aspect of an actual (intentional or accidental) release of a live microbe. It might be rejected by the established members of a given environmental or symbiotic (appendage) microbiome, which occupy similar or identical niches. But it may also reshape and disturb a commensal microbiome, turning it pathogenic, or transform some of its members into more aggressive and/or pathogenic varieties through horizontal gene transfer. Such a delicate fusion of pathogenicity with ecology poses the greatest biosecurity challenge that Bioresilience 2.0 strives to address.

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