Review

Turning Pathogens into Transmissible Vaccines via Loss-of-Function Research and Interferon Gene Insertion: Trampling Death by Death?

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Turning Pathogens into Transmissible Vaccines via Loss-of-Function Research and Interferon Gene Insertion: Trampling Death by Death?

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Abstract: Throughout several centuries, infectious pathogenic agents have been used as models for the ongoing efforts of vaccine development, which saved hundreds of millions of lives from life-threatening infectious diseases worldwide. Nonetheless, there has been a missing gap that various polymorphic microbes have been taking advantage of in their evolutionary pathway: the interferon system, which often prevented the timely activation of second and third-line host immunity, leading to chaotic and mismatching immune responses. The phenomenon of increased incubation period of various infectious diseases may be a result of the increased abilities of such microbial agents to directly and indirectly undergo molecular self-camouflaging, which prevents the activation of Type I and Type III Interferon-encoding genes (INGs) in indirect and direct manners respectively, and cleaves the mRNA molecules encoding such interferon glycoproteins, often causing major delays in the process of autocrine and paracrine signalling of Type I and Type III Interferon glycoproteins, which in turn allows an unrestricted, exponential increase of the microbial load/count, giving rise to a statistical probability that the quality of the delayed immune response will be low and contributory to the processes of pathogenesis and pathophysiology. Some microbial proteins as such also inhibit the translation of Interferon-Stimulated Genes, thereby substantially affecting the signalling rates within the cytokine system and often bringing a negative domino effect upon the activation rates of the adaptive immune system. Apprehending the foundational layer of the current problems in evolutionary microbiology, epidemiology and public health studies is most likely crucial for the course of immunological, pharmaceutical and vaccine-related clinical research. In the current case, it is the complex set of molecular capabilities to suppress Type I and Type III Interferon-based signalling displayed by several polymorphic microbes of public health concern, and it may be that the rates of immunopathogenesis induced by such microbes are directly proportional with such pathogenic abilities of induced interferon suppression. Proportional medical responses could include the development of approaches involving low dosages of human recombinant Type I and Type III Interferon glycoprotein and perhaps also of protollin in the nasopharyngeal cavity, potentially bringing an example of putting a novel concept of a "United Immune System" into practice. Furthermore, similar dosages of such interferons could be administered into human immune cells including plasmacytoid dendritic cells, as well as natural and adaptive lymphocytes, to optimise their immune function and integrity against various environmental hazards. Ultimately, clinical researchers may isolate the pathogenic agents, attenuate them through the process of loss-of-function laboratory research, before performing gene editing to insert Type I, Type III and perhaps also Type IV Interferon-encoding, perhaps as well as Pattern Recognition Receptor (PRR) Agonist-encoding genes that specifically match the PRR targeted by the implicated microbes, into their genomic profile and potentially releasing the genetically-modified pathogens back into the environment transmissible factories of Type I and Type III Interferons, perhaps as well as of specific PRR Agonist proteins, which could include outer membrane proteins from the B serogroup of *Neisseria meningitidis* bacteria. If the microbial genetic activities implicating evasion of the interferon system are too intense and multilateral, at least some of the microbial genes responsible for such activity could be permanently removed in some exchange with the human genes encoding major elements of the interferon system that would be inserted into the microbial genome afterward. It may be important

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to mention that the process of clinical weakening of the isolated microbes would be aimed at reducing the activity of microbial genes implicated in pathogenesis and pathophysiology, and perhaps not as much microbial genes involved in reproduction and transmission. Such a change may bring various pathogenic agents into a path of evolutionary self-destruction, as they would start producing and sending signals to the proximal, innate immune system as soon as they enter the first host cells, making their same processes of induced innate immune suppression ineffective, and several dilemmas in microbial evolution could ultimately be tackled as a result, possibly even at least attenuating the phenomenon of acquired antibiotic resistance by various pathogenic bacteria. A clinical approach as such is likely based on the model of increasing the accessibility to insulin-based treatment against Diabetes Mellitus via insulin-encoding gene insertion into the genomes of harmless bacteria prior to their administration into human host organisms, which saved millions of lives worldwide. Processes of shrinkage of any level of limitations to potential efficacy would include the manual utilisation of inhalators, oral drops and/or injectable serums containing such modified microbes to ensure that such an immunising effect would be conferred simultaneously with exposure to the artificially-changed genetic version of the microbe, effectively creating an "active evolutionary trap" for the pathogens, potentially resulting in their gradual de-selection whilst they continue to transmit just sufficiently enough to produce lasting immune memory. In other words, a phenomenon of "pathogen baptism" could occur, implicating a domination of "domestic variants" over wild-type variants in the environment, with the former becoming like "wild animals", as they would remain the only virulent pathogenic variants and gradually even become extinct, with the "domestic" variants becoming dominant, according to the viral quasispecies theory. This set of clinical responses, including targeted immunoediting and gene vector strategies, can be analogized to a strategic operation against a mega-hurricane. The immune system, overwhelmed by storm-like chaos, cannot function effectively from the outside. Thus, medical intervention must act like military aircraft entering the eye of the storm from above—where calm resides—not to be engulfed, but to deploy stabilizing agents from within the calm zone. Only then can the storm's structure be undone without triggering systemic devastation. A conquest from within, while remaining of another world. A set of clinical responses involving all such pathways may ultimately bring a promise of a health-related "Golden Age" throughout the world, with DeepSearch Artificial Intelligence (AI)-generated mathematical models indicating a significant probability that such a scenario would occur under real-world conditions, whilst emphasising upon the high importance of the existence of thoroughly rigorous clinical testing steps and procedures to ensure no harm is caused in any such proposed candidate approaches, and to make sure that the world populations reach a full extent of informed consent.

Keywords: innate immunity; adaptive immunity; evolutionary microbiology; evolutionary immunology; virus; bacterium; yeast; pattern recognition receptors; interferon system; lymphocyte system; polymorphic microbes; single-nucleotide polymorphism; molecular self-camouflaging; loss-of-function research; gene editing; antibiotic resistance; cytosol; medical ethics; prophylaxis; therapeutics; gene expression; protein synthesis; autocrine signalling; paracrine signalling; transmissible immune factories; artificial intelligence; bioethics; informed consent; triumph within

Introduction

Recently, several public health incidents have occurred and significantly impacted the health state of both animal and human host organisms. The highly diverse phenomena of molecular self-camouflaging displayed the causative microbial agents may represent a foundational factor for the induced severity of infectious clinical disease in both animal and human hosts, which seems to surpass the current version of vaccine-based clinical responses, despite their high rates of efficacy displayed throughout the past centuries. It may be that there is an existing gap of potential update in the domain of vaccinology - one that would directly antagonise such a foundational factor of induced

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severe infectious illness. Given the fact that natural immunity has recently been shown to exhibit traits of specificity and even its own, distinct "specific memory" as well makes it possible for the efforts of vaccinology to be updated through a wider inclusion of both first-line and second-line, natural immune elements. Such an aspect may only confirm the high rates of efficacy and safety displayed by recently-developed prophylactic and early therapeutic approaches involving low dosages of human recombinant Type I and Type III Interferon glycoproteins into the nasopharyngeal cavity. Interestingly, results indicate that such concentrations of Type I and Type III Interferon glycoprotein brought effects of immunostimulation, immunomodulation and even whole effects of immunisation against multiple diseases, including COVID-19, flu, AIDS and various oncological diseases. Moreover, it has been suggested that protollin brings similar immunostimulatory and immunomodulatory effects in the case of Alzheimer's Disease, by the recruitment of adaptive lymphocytes to areas of the Central Nervous System, where they will in turn activate microglial cells and oligodendrocytes before misfolded alpha-synuclein and beta-amyloid toxins start causing clinical signs and symptoms (Frenkel D. et al., 2008). Scientists theorised that protollin brings an immunisation effect against the pathogenesis and early pathophysiology of Alzheimer's Disease, potentially giving further rise to the probability that Type I and Type III Interferons bring similar effects (Frenkel D. et al., 2005). A similar outcome may occur for the case of Retinitis Pigmentosa, which is caused by misfolded Rhodopsin toxins in the process of a progressive destruction of retinal cells with rods, which is clinically manifested as a progressive loss of vision to the point of the patient reaching a state of complete blindness, often by mid-age adulthood and, in such cases, a medical approach involving the administration of chaperones specific to the retinal tissue may be required as well. Furthermore, it is possible for plasmacytoid Dendritic Cells (pDCs), Natural Killer (NK) Cells, helper CD4+ T-Lymphocytes and cytotoxic CD8+ T-lymphocytes to be treated with a low dosage of Type I and Type III Interferons, perhaps alongside protollin, to improve both their efficacy and integrity against environmental hazards, and such an approach would effectively represent a form of "immunisation of immunising agents" and could potentially turn adaptive lymphocytes into "super-lymphocytes" in efforts to protect human immunity from the long-term and life-threatening danger of HIV-1-induced AIDS, and essentially conferring a proportional "punch of immunological self-defence" against the virus (Carp T., 2024). Interestingly, there could be a scenario in which self-replicating viral vectors not inductive of virulence and containing inserted Type I and Type III IFN-encoding genes and containing at least the majority of the genetic information of the HIV-1 retrovirus would be used as self-replicating vaccine candidates against HIV-1-induced AIDS, given that the central elements of the adaptive immune system, helper CD4+ and cytotoxic CD8+ T-Lymphocytes are primarily targeted by the HIV-1 retrovirus and that their first-line and second-line immunity requires a sharper prophylactic and early therapeutic sensitisation (Carp T., 2025).

Given the fact that the interferon system may be calibrated likewise to help human immunity develop a proportional evolutionary response that would preserve human health over microbial self-camouflaging capabilities, it is possible for vaccine researchers and developers to include Type I and Type III Interferon-encoding genes into live-attenuated pathogens or pathogenic fragments. Furthermore, it is possible for researchers to perform similar gene editing procedures in isolated microbes to turn microbial agents into signalling facilities for the host innate immunity, which would essentially mean that pathogens as such would be effectively transformed into vaccines, as they would become unable to cause disease given the automatic microbial autocrine and paracrine signalling of both Type I and Type III Interferon glycoproteins once it undergoes the first series of receptor-mediated endocytosis. Given the fact that the first and the third classes of the interferon system profoundly stimulate and modulate major immune responses, essentially representing the foundation for the adequate activation of the entire immune system following the first stages of infection, it may be that such a scenario may apply even for pathogenic agents causative of diseases of more significant public health concern. Likewise, with the unprecedented threats made by recent developments contained within the evolutionary path of pathogenic agents, there seems to be a small, but considerable window of opportunity that may bring unprecedented hope, with the possibility of

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artificially inducing genetic manipulation of newly-selected variants of microbial agents that constitute a concern for both human and animal public health, ultimately making it unnecessary for the pharmaceutical industry to develop nasopharyngeal spray or drop-based vaccine approaches, let alone traditional needle-based ones. In other words, the ultimate stage of vaccine evolution may involve a silent "infection" of human and animal hosts with attenuated microbes that contain active Type I and Type III Interferon-encoding genes, which produce a number of interferon glycoprotein that significantly crosses a threshold level characterised by the ability of the same pathogen to antagonise them. Poetically, just as advanced stages of microbial evolution hijacked and suppressed the quality of human immune responses via favouring the development of autoimmunity, so artificial interventions will lead to advanced stages of human and animal immune evolution by the induction of microbial activities that antagonise each other. If problems of inefficacy occur due to a lack of a threshold level of human-to-human and animal-to-animal transmission of such attenuated, interferon-encoding microbial agents, then inhalators or injectable serums containing low concentrations of such microbial copies may be administered to patients during the first weeks of the fall season to manually induce an immunising effect where gaps preventing the reach of herd immunity may exist.

Discussion

Tackling the complex microbial machinery of induced immune evasion most likely represents the primary objective of public health and vaccine innovation-based pharmaceutical, scientific and clinical research. There is a highly diverse group of candidate clinical approaches that can help the human immune system outcompete the novel extents of induced immune evasion by several polymorphic microbes, and such approaches may be used even in combination to foster the production of utmost qualitative and long-lasting results for the human and animal immune systems alike. It may be that the ultimate solution to the dilemma of viral and bacterial immune evasion is the isolation, attenuation and genetic editing of epidemic microbes during their initial stages of distribution throughout human and animal populations respectively, which commonly occurs during the first weeks of the fall season. Despite the fact that microbial agents utilise highly diverse methods of inducing cellular and tissue-level pathogenesis and pathophysiology, there seems to be a Universal method of immune evasion utilised by the majority of such microbes in their preparation for inducing clinical disease. The machinery of induced immune escape generally consists of three distinct pathways, which all ultimately point to the common result of significantly suppressing the production and signalling of Type I and Type III Interferon glycoproteins. The first pathway constitutes a direct form of microbial self-camouflaging and involves the double methylation of the 5′ end of the microbial genome by two viral non-structural protein complexes (NSP10/14 and NSP10/16 respectively, with NSP10 representing the activator protein and NSP14 and NSP16 representing the effector proteins), which leads to the prevention of Pattern Recognition Receptor (PRR)-based recognition of Pattern-Associated Molecular Patterns (PAMPs) on the microbial genome, as well as of Damage-Associated Molecular Patterns (DAMPs), which represent toxin proteins synthesised by the microbial genome once it has undergone receptor-mediated endocytosis without significant restriction. Given the existence of indirect, transient immunosuppressive methods as such, active genes encoding PRR agonists specific to the type of PRR inactivated by the pathogenic microbe could also be inserted into the microbial genome, perhaps to ensure proportion in the interferon-stimulatory and interferon-stimulated signalling rates in all cases. The second pathway represents an indirect form of microbial self-camouflaging, which however involves the direct antagonism of Type I and Type III Interferon-encoding genes (INGs), as well as of Interferon-Stimulated Genes (ISGs) through various methodologies of mRNA cleaving and induced protein disposal - particularly by translated non-structural proteins (NSPs) 1 and 2. The third pathway involves the facilitation of the viral protein-based paracrine signalling through channeling nanotubes, which are produced by host cells with the original purpose of transmitting immune signals as soon as the first infection stages occur. Likewise, microbial agents of individual and public health concern

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have generally developed highly profound networks of immune evasion and even suppression, stimulating scientific and pharmaceutical researchers to develop unprecedented, world-class methodologies of clinical responses that "outsmart" such networks contained by the evolutionary machinery of viruses, bacteria and even yeasts.

Generally, it is known that the cytokine system of the innate immune system constitutes the root of the entire process of adaptive immune activation and signalling that is proportional to the extent and severity of the microbial reproductive rates within the host organism. Nonetheless, it may be important to differentiate the first and the third classes of the interferon system from the second class, due to the fact that the production and signalling of Type II Interferons is directly dependent upon the production and signalling of Type I and Type III Interferons. Namely, it is known that Interferon-Stimulated Gene products, which are signalled as a direct result of adequate Type I and Type III Interferon signalling, are responsible for the recruitment of Natural Killer Cells, which constitute factories for Type II Interferons. Likewise, it may be more contextual for the research communities to deem Type I and Type III Interferon glycoprotein as pre-cytokine innate immune elements and potentially raise clinical awareness about the particularly high importance such particular interferon glycoprotein types brings in the activation process of the immune system, as they constitute a foundational factor for the adequate activation of the cytokine system itself. Moreover, the fact that the innate immune system displays considerable extents of "specific memory", as well as considerable traits of specificity in their signalling processes, ultimately indicates the existence of adaptive immunity-like "purpose" even within its first line of defence, which comprises the PRR system, as well as the pre-cytokine networks of INGs and ISGs. Given the fact that innate immunity has shown to display considerable extents of "specific memory", as well as specificity in their activation and signalling processes, Likewise, innate immunity may also be used significantly in the process of immune system-based vaccine innovation and development, despite the development of the initial theory that important elements of the innate immunity may only be used as vaccine adjuvants (Carp T., 2024). Furthermore, recent clinical research efforts performed in China involved the discovery of another class of interferons in zebrafish; Type IV Interferons. Given the fact that IL10R2 was found to be a common receptor for Type III and Type IV Interferons, it is likely that the fourth class of interferons represents part of the pre-cytokine elements of natural immunity alongside Type I and Type III Interferons, meaning that they could be included in the list of genes that could be inserted into such microbial genomes. Such developments ultimately indicate that principal elements of first-line, innate immunity also play visible roles in whole processes of immunisation as well, and not solely the second line of natural immunity. Hence, infectious pathogens may be isolated, undergo loss-of-function research in various laboratory settings, specifically by having their pathogenesis-inducing and pathophysiology-maintaining genes substantially attenuated, whilst probably not having their genes involved in microbial reproduction and transmission substantially attenuated as well, prior to having Type I and Type III Interferon glycoprotein-encoding genes inserted into their genome, and being released back into the surrounding environment as transformed, immunising agents that have become factories for Type I and Type III Interferons, and that may be transmitted in an airborne manner. There may still be some existing limitations in such a case, as there ought to be some form of transmission in order for herd immunity to be reached, and that may only occur if there is some extent of clinical symptoms occurring following such microbial exposures, and the interferon-encoding genes may prevent the development of symptoms, potentially making a significant number of the copies of the genetically-modified microbes unable to be transmitted. Perhaps, a low concentration of genetically modified microbial copies can be inhaled nasally by and/or administered via oral drops to a given number of human and animal recipients in order for herd immunity to be manually reached if necessary. In other cases, low concentrations of genetically modified microbial agents as such may be placed into an injectable serum, prior to being administered intramuscularly, in a similar fashion to traditional, intramuscular vaccination. Another advantage of such an overall set of potential approaches represents the fact that human interferon-alpha, -beta and -lambda-encoding genes contain an approximate total of 1,518 base pairs (bp), which generally represents a

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proportion of 0.1-10% of major microbial genomes, meaning that the probability of the existence of limitations with regards to potential negative effects to microbial genomic capacity is pronouncedly low, even if genes encoding agonists of human and animal Pattern Recognition Receptors (PRRs) are included in the process of microbial gene insertion. In any, most likely remote cases of limitations, one or two interferon subtype-encoding genes may be inserted instead of three, for example. The ultimate objective of such candidate vaccination approaches is to help both humans and animals outcompete the gained evolutionary capabilities of several microbial agents through direct and indirect methods of molecular self-camouflaging whilst keeping the extent of safety above the threshold level established by the Universal principles of medical ethics. Such a candidate clinical approach is likely based on the model used in past efforts to exponentially increase the bioavailability and biodistribution of insulin for patients suffering from Type I and Type II Diabetes Mellitus, which occurred via the utilisation of harmless bacteria containing recombinant genes encoding insulin, effectively transforming them into "mobile factories" of insulin (Riggs A. D., 2021). Through such a procedure, millions of lives were saved worldwide, as bacterial genes encoding insulin were reproduced and distributed sharply with each round of bacterial binary fission. Likewise, such a process of bacterial gene editing utilised for prophylactic or therapeutic approaches in humans and animals is not completely foreign to the scientific and medical communities. Perhaps, insertion of genes encoding Type I and Type III Interferons, as well as protollin, chaperones that play a role in the maintenance of retinal integrity, as well as wild-type Rhodopsin can be inserted into the genomes of such harmless bacteria, before they would be administered through eye drops or nasal sprays for the purpose of attempting prophylactic and/or early therapeutic approaches against the extracerebral proteinopathy of Retinitis Pigmentosa, for example (Kosmaoglou M. et al., 2008). Finally, somatic STEM cells could be inserted into the retinal tissue, where they would differentiate and mature into cells with rod photoreceptors, to attempt a replacement of the retinal cells responsible for the conversion of UV light into an electrical signal via phototransduction, that had been damaged and destroyed by Rhodopsin aggregates, with novel rod photoreceptor-containing cells (Roy, S. and Nagrale, P., 2022). Such an approach could at least sometimes even prevent the onset of the disease.

Harmless bacteria, like some serotypes of Escherichia coli, underwent genetic manipulation to start synthesising human insulin after the human INS gene, which encodes the hormone protein, is introduced into the bacterial genome, and the CRISPR-Cas9 technology was used in the process of bacterial gene editing via the utilisation of plasmids and of distinct restriction endonucleases. It is known that different restriction endonucleases are utilised for different binding sites upon the bacterial and human DNA. A positive aspect of such a fact is that the human ING genes are generally significantly shorter in size than the human INS gene, given that human interferon-alpha-, interferon-beta- and interferon-delta-encoding genes altogether consist of approximately 1,518 bp, which is approximately 9.22 times shorter than the size of the human INS gene, which is of a size approximated to 14 kilobases (kb; 1 kb = 1,000 bp). Genes encoding proteins on the outer membrane of the B serotype of *Neisseria meningitidis* bacteria that are part of the Protollin immunostimulatory agent have a similar length to each of the genes encoding the interferon subtypes in cause. Such an aspect may be crucial to mention given the fact that viruses are generally substantially shorter in genomic size than bacteria, considering the example that some viruses have genome lengths that are barely higher than the INS gene length. Perhaps, live-attenuated *Neisseria meningitidis* bacteria would particularly stimulate the interferon system due to its protein components upon the outer membrane, which likely play a stimulatory factor for the activation of Toll-Like Receptors (TLRs) 2 and 4. Such bacteria could also undergo CRISPR-Cas9 gene editing to have Type I, Type III and perhaps Type IV IFN-encoding genes into their genome. Interestingly, it was even discovered that interferons synthesised by human genes played major prophylactic roles against viral infections in plants (Orchansky, P., Rubinstein, M., and Sela, I., 1982).

If genes suppressive of the interferon system are too problematic, at least some microbial genes encoding proteins directly and/or indirectly suppressive of various elements of the interferon system could be permanently removed from the microbial genome. For example, in various coronaviruses,

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two viral genes encoding nsp1 and nsp10 respectively could be permanently extracted from the viral genome and in change, genes encoding IFN-alpha, -beta and -lambda could be inserted into the viral genome, perhaps in a genomic spot that is approximately the same as the one previously occupied by the nsp1- and nsp10-encoding genes, since the genetic length of the three IFN subtypes altogether (~1,518 bp) is not significantly greater than the genetic length of the two viral genes added together (~1,020 bp). Or, at least nsp10 could be permanently extracted, since its production determines whether nsp14 and nsp16 will be activated via molecular interaction with nsp10, which would form the two methyltransferase enzymes that double cap the 5′ end of the viral genetic material, preventing the recognition of the virus as pathogenic by the Pattern Recognition Receptors upon and inside many host cells. The objective of such an approach would be for the genetically-modified and attenuated microbes to still trigger an existing immune response and have existing reproductive rates that would cross the threshold level of human-to-human transmission, to ensure that the created microbial factories for the interferon system to be distributed as much as possible, to ultimately confer an effect of herd immunity without the causation of actual disease morbidity. In order for such events to occur, a restricted rate of indirect and/or direct viral self-camouflaging might still need to occur, though such a rate must not be even closely as high as the rate of interferon production by the genetically-modified and virulence induction-attenuated microbes. In short, the induction of such an epidemiological effect might naturally lead viruses to their evolutionary decay whilst helping human immunity develop long-lasting antimicrobial memory without the causation of clinical disease. The fact that SARS-CoV-2 induced subclinical, "clinically-invisible" inflammatory effects that were detected following clinical screening tests that included Computer-Tomography (CT) scans of the lower respiratory tract during the asymptomatic/presymptomatic stage of COVID-19 may show that such a gap of induced immune response with an absence of clinical disease is in fact possible and could be used as a potential error bar in the current model of vaccine innovation and refinement, as there is in fact no harm caused in such a process. In other words, if there would be any causation of inflammatory responses, they would be transient, not occurring in the key areas of the organism for the maintenance of the general state of health and of life, and not any more intensive than the sub-clinical signs observed in the respiratory tracts of patients with asymptomatic COVID-19 (Romeih, M., Mahrous, M. R. and El Kassas, M., 2022).

There are multiple existing environmental approaches of weakening specific microbes, by physical, chemical, biological and/or genetic manners, to make them more tolerable by the host organisms, with the purpose of encouraging the production of a herd immunity level without the causation of individual, life-threatening forms of infectious disease in the process. Nonetheless, few would barely pass the bioethical screening procedures because the ultimate purpose of medicine is to first not cause any form of harm. Nonetheless, it has become possible to utilise such approaches in the specific context of added Type I and Type III Interferon-encoding genes into the genomic profile of the microbial agent, as there would be no harm induced any longer due to the fact that the pathogen would automatically produce the glycoprotein molecules that produce the adequate anti-microbial signals whilst maintaining the adequate balance between produced anti-inflammatory and pro-inflammatory signals. Such approaches would require due clinical testing if a direct, separate administration of Type I and Type III Interferon glycoproteins does not bring the required long-term effects of immunisation whilst keeping financial expenditure to a level as low as the case of the vaccination campaigns against various epidemic illnesses that have been occurring for the past century. Interestingly enough, it is such a missing "piece of puzzle" existent in research ideas concerning loss-of-function microbial research that seems to fill in a proportional gap in human and animal vaccinology, as the host interferon system represents the primary target of microbial adaptation via multiple single-nucleotide polymorphism events in various functional areas of their genome. Another example of a clinical application may be in the tackling of antibiotic-resistant bacterial infections due to the fact that the foundation of the issue lies within evolutionary biology, like the dilemma of evolved, interferon-evading microbial mechanisms. It may ultimately be less financially demanding for such an application to be widely performed in antibiotic resistant bacteria

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of individual and public health concern, by having their pathogenic genes attenuated and two or three subtypes of genes encoding Type I and Type III Interferons inserted into the bacterial genome. In short, due to the foundational role played by first-line immunity, it may be that a widespread utilisation of Type I and Type III Interferon-based clinical applications may tackle complex modern-day health-related problems that include acquired antibiotic resistant by bacteria, perhaps due to an existing level of excess antibiotic usage and distribution in several areas of the world and particularly in hospital settings, where secondary bacterial infections are deemed as common and safety often turns to be placed above the necessity of medical solutions to be projected and applied according to the matched aetiological context of the involved clinical disease.

Navigating the Eye of the Pathogenic “Mega-Hurricane” (Its Genomic-Proteomic Evolution) — A Metaphorical Framework for Innovative Immunological Interventions

In the evolving battle between host immunity and microbial adaptation, pathogens have increasingly demonstrated sophisticated genomic and proteomic strategies to subvert immune recognition. Chief among these is the suppression of Type I and Type III interferon responses—crucial to early antiviral and antibacterial defense. This suppression creates what can metaphorically be described as the "eye of the hurricane": a deceptively quiet molecular zone in which the host immune system is rendered momentarily unaware of an encroaching microbial storm. Here, the pathogen is not simply evading detection; it is actively constructing an immunological null zone—camouflaging its presence at the genetic and post-transcriptional levels to delay immune escalation.

An analogy of defeating a mega-hurricane by entering its eye from above—used to describe the proposed interferon-based intervention model—offers a powerful metaphor for reconceptualizing therapeutic strategies against highly evolved, immunosuppressive pathogens. Like the strategic entry of an aircraft into the calm center of a hurricane to release neutralizing agents, the method of immune reactivation described here relies not on brute immunological force, but on calculated, precision-guided intervention. This represents a philosophical pivot: the transition from reactionary to anticipatory medicine, where microbial evasion is met not with escalation, but with symbolic subversion. Such an analogy carries weight at multiple levels. At the biological level, the “eye of the hurricane” mirrors the microbe-induced immune silence: a space carved out by pathogenic suppression of interferon signalling, which renders the immune system blind during the early phases of infection. Within this molecular calm, the pathogen multiplies unchallenged, much as a hurricane intensifies while its eye preserves equilibrium. The proposed strategy—introducing gene-edited vectors or live-attenuated, immune-activating microbes—aims to penetrate this silence and reawaken host defences from within, ideally without triggering a cytokine storm or collateral tissue damage. From a systems perspective, this represents a significant evolution in immunological architecture. Rather than relying solely on direct pathogen eradication, the model prescribes the strategic introduction of interferon signaling at the molecular "quiet zone"—a conceptual sanctuary untouched by conventional immune tactics. This not only avoids antagonizing the storm (i.e., overactivation of inflammatory pathways), but utilizes the storm’s own structure (immunosuppressive calm) as an entry point for neutralization. It becomes a *hacking of the hurricane’s physics*. Philosophically, this draws on ancient traditions of “victory through inversion,” where transformation occurs not by overpowering the enemy, but by becoming a different kind of presence within its world. This is echoed in Eastern philosophies of *wu wei* (non-action as highest form of action), and in Christian mystical theology (e.g., St. John of the Cross’s concept of divine work in the “dark night of the soul”). It is also structurally akin to the Platonic descent into the cave — not to fight shadows, but to light a fire within them.

The analogy of deploying military aircraft into the eye of a mega-hurricane to neutralize it from within offers a compelling metaphor for contemporary strategies in combating polymorphic pathogens. Just as the eye of a hurricane represents a deceptive calm amidst surrounding chaos, certain pathogens exploit similar mechanisms by creating molecular 'calm zones' within the host, evading immune detection and delaying response. This strategic evasion mirrors the hurricane's eye, where the storm's most destructive forces are temporarily absent, yet the surrounding turmoil

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persists. In this context, the proposed immunological interventions—such as the administration of low-dose recombinant Type I and III interferons or the introduction of genetically modified microbes—can be viewed as analogous to the aircraft's mission. These interventions aim to penetrate the pathogen's protective mechanisms, delivering targeted responses that disrupt its internal equilibrium without triggering widespread immune activation, thereby minimizing collateral damage to host tissues. Philosophically, this approach resonates with Ralph Waldo Emerson's concept of the "transparent eyeball," wherein the observer becomes one with the observed, absorbing all without distortion . Similarly, the immune system, through these interventions, becomes attuned to the pathogen's internal environment, responding with precision and harmony. Furthermore, this strategy aligns with the principles of experientialism, emphasizing the importance of context and embodied experience in understanding and responding to complex phenomena. Gilbert Simondon's theory of *individuation* offers a theoretical frame for such targeted biological action. For Simondon, identity is constituted through transductive processes—dynamic relational events rather than static essences. In this light, the host-pathogen interface is not a fixed battleground but a site of potential reconfiguration. Introducing altered immunological stimuli—especially gene-edited microbes or precision interferon payloads—within the eye of the pathogen's immunological suppression can reindividuate the host immune system's response. It ceases to be a delayed echo and becomes a co-evolving presence. The strategic elegance of this approach also reflects Sun Tzu's *Art of War*, particularly the principle of "winning without fighting." Rather than assaulting the pathogen's defenses directly, the immune system, supported by synthetic intervention, enters the very space the pathogen believes to be under its control—disrupting from within. This is a reversal not only of power but of paradigm: healing no longer occurs by dominance, but by infiltration, resonance, and symbolic redirection.

In immunological terms, such an approach might involve the synthetic delivery of interferon-encoding constructs into host cells via inhalable, ingestible, or injectable vectors—tools that can inhabit the nasopharyngeal and mucosal environments with minimal systemic activation. These vectors, akin to conceptual aircraft, can carry genomic payloads that counteract microbial stealth mechanisms. Importantly, these payloads may be informed by the viral quasispecies theory, intentionally shaping the pathogen's mutational landscape toward less virulent, more immunogenic strains. The process becomes not just therapeutic, but *evolutionarily formative*. Moreover, this model opens pathways for addressing antibiotic resistance and pathogen persistence. By converting the evolutionary pressure from pharmacological elimination to immunological co-option, microbial populations may be directed toward self-destruction or domestication. This "pathogen baptism," to borrow the metaphor from Theodor Carp, reframes the microbe not as enemy, but as reluctant emissary of its own undoing. Through evolutionary judo, the force of microbial survival becomes the trigger for its neutralization. The practical execution of this model requires deep genomic and proteomic surveillance, coupled with AI-driven predictions of microbial evasion pathways. However, its ethical implications are equally pressing. Such interventions must be transparently regulated, informed by rigorous preclinical data, and introduced under conditions of informed consent and international consensus. Like pilots entering the hurricane's eye, researchers must tread with precision, humility, and a commitment to do no harm.

This symbolic and strategic hybridization aligns with a new transdisciplinary model of biomedical ethics: one in which intervention must be not only scientifically effective, but also philosophically coherent and ecologically proportional. In this regard, "conquest from within" can be interpreted as a paradigm of non-invasive sovereignty—an intervention that integrates with host biology, respects systemic equilibrium, and shifts the evolutionary arc away from antagonism toward integration. Such an approach resonates with current bio philosophical discourses, particularly those of Gilbert Simondon, who emphasized individuation through relational tension rather than opposition. The modified microbe becomes a *mediator*, not an invader—a transitional form that reawakens immune awareness without sparking immune alarm. From the perspective of the immune system, it is as though the storm had chosen to dissolve itself. Finally, the hurricane analogy also

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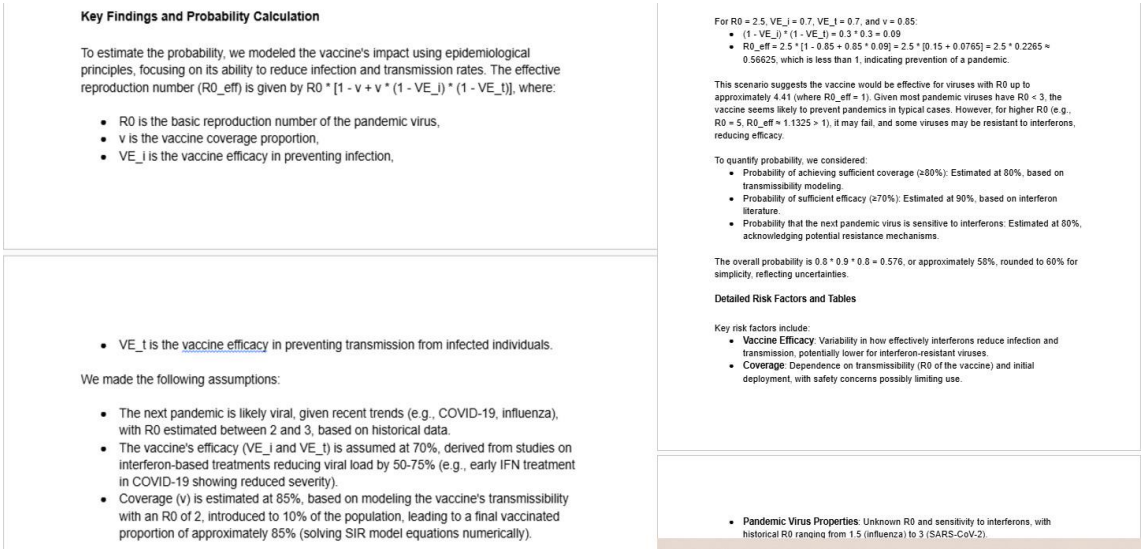
gestures toward emerging frameworks in planetary health and evolutionary epidemiology. Just as geoengineering strategies seek to modulate climate from within its feedback loops, biomedical geo-strategies must learn to modulate pandemics through internal microbial feedback disruption. The future of infectious disease control may no longer lie in building bigger barricades, but in learning to plant resilient seeds within microbial systems themselves.



Key Findings and Probability Calculation

To estimate the probability, we modeled the vaccine's impact using epidemiological principles, focusing on its ability to reduce infection and transmission rates. The effective reproduction number (R0_eff) is given by R0 * [1 - v + v * (1 - VE_i) * (1 - VE_t)], where:

- R0 is the basic reproduction number of the pandemic virus,
- v is the vaccine coverage proportion,
- VE_i is the vaccine efficacy in preventing infection,
- VE_t is the vaccine efficacy in preventing transmission from infected individuals.

We made the following assumptions:

- The next pandemic is likely viral, given recent trends (e.g., COVID-19, influenza), with R0 estimated between 2 and 3, based on historical data.
- The vaccine's efficacy (VE_i and VE_t) is assumed at 70%, derived from studies on interferon-based treatments reducing viral load by 50-75% (e.g., early IFN treatment in COVID-19 showing reduced severity).
- Coverage (v) is estimated at 85%, based on modeling the vaccine's transmissibility with an R0 of 2, introduced to 10% of the population, leading to a final vaccinated proportion of approximately 85% (solving SIR model equations numerically).

For R0 = 2.5, VE_i = 0.7, VE_t = 0.7, and v = 0.85:

- (1 - VE_i) * (1 - VE_t) = 0.3 * 0.3 = 0.09
- R0_eff = 2.5 * [1 - 0.85 + 0.85 * 0.09] = 2.5 * [0.15 + 0.0765] = 2.5 * 0.2265 ≈ 0.56625, which is less than 1, indicating prevention of a pandemic.

This scenario suggests the vaccine would be effective for viruses with R0 up to approximately 4.41 (where R0_eff = 1). Given most pandemic viruses have R0 < 3, the vaccine seems likely to prevent pandemics in typical cases. However, for higher R0 (e.g., R0 = 5, R0_eff ≈ 1.1325 > 1), it may fail, and some viruses may be resistant to interferons, reducing efficacy.

To quantify probability, we considered:

- Probability of achieving sufficient coverage (≥80%): Estimated at 80%, based on transmissibility modeling.
- Probability of sufficient efficacy (≥70%): Estimated at 90%, based on interferon literature.
- Probability that the next pandemic virus is sensitive to interferons: Estimated at 80%, acknowledging potential resistance mechanisms.

The overall probability is 0.8 * 0.9 * 0.8 = 0.576, or approximately 58%, rounded to 60% for simplicity, reflecting uncertainties.

Detailed Risk Factors and Tables

Key risk factors include:

- **Vaccine Efficacy**: Variability in how effectively interferons reduce infection and transmission, potentially lower for interferon-resistant viruses.
- **Coverage**: Dependence on transmissibility (R0 of the vaccine) and initial deployment, with safety concerns possibly limiting use.
- **Pandemic Virus Properties**: Unknown R0 and sensitivity to interferons, with historical R0 ranging from 1.5 (influenza) to 3 (SARS-CoV-2).

Figure 1. Grok 3 beta, DeepSearch AI-generated response mentioning a mathematical modelling approach applied into epidemiology, utilising scientific evidence from peer-reviewed immunological and microbiological studies.

According to mathematical models created by novel versions of **Artificial Intelligence** (i.e. **Grok 3 beta's DeepSearch** and **DeeperSearch** functions) and applied into theoretical immunology and epidemiology, there may be an existing 60% probability that such a CRISPR-Cas9 gene editing-based approach will successfully prevent the onset of the next pandemic. Mathematical formulae utilised in epidemiological and public health-related research were utilised by DeepSearch AI in such a process and in the end, the model confirmed an existing possibility that pathogens may effectively become "domesticated" and that wild-type, dangerous variants will eventually become naturally deselected in such a process, as the domestic variants will outcompete the wild-type variants. Two ChatGPT models (GPT-4o and a Deep Research model) were also utilised to verify the methods developed by the Grok 3 DeepSearch-generated mathematical models, which confirmed the existence of significant theoretical probabilities of at least similar outcomes. Furthermore, such AI modelling was utilised to compare the mentioned natural transmission-based, self-replicating CRISPR-Cas9 vaccine candidate with more traditional methods, such as existing mRNA-based vaccines with regards to their probability of successfully preventing the next pandemic and that a virus would most likely cause the next pandemic under current societal and public health-related conditions. It was theoretically suggested that the natural transmission-based method would have a considerably higher probability of successfully preventing the next pandemic than the mRNA approaches (i.e. around 40%), and it was overall indicated that it would have a strong potential of saving millions of lives and trillions in global economy, effectively changing the nature of pandemic prevention strategies.

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In contrast, Carp's natural transmission approach could theoretically achieve higher coverage without these barriers, supporting the 60% probability. However, both approaches are theoretical, and Carp's method requires validation through clinical trials, which is not yet evident as of March 2025 Theodor-Nicolae Carp ResearchGate Profile.

Comparative Analysis: Factors Influencing Probability

To organize the factors, consider the following table comparing Carp's CRISPR-Cas9 approach and mRNA vaccines under current context:

Factor	Carp's CRISPR-Cas9 Approach (Natural Transmission)	mRNA Vaccines
Current Stage	Theoretical, early-stage, no clinical trials	Proven effective for COVID-19, widely deployed
Probability Claim	60% theoretical, based on models	Estimated 35-40% under current challenges
Financial Impact	Reduced need for rollout, but high development costs	High production and distribution costs, funding gaps
Geopolitical Impact	Potential to bypass nationalism, but ethical risks	Disrupted by nationalism, supply chain issues
Safety and Ethics	Uncontrolled spread raises concerns, needs validation	Established safety profile, but distribution uneven
Coverage Potential	High, through natural spread	Limited by access and acceptance, often <70% in LICs

Figure 2. Grok 3 beta (DeepSearch) AI-generated answer bringing an explained theoretical comparison between such transmissible, potential vaccine candidates and more traditional, mRNA-based vaccines in their potential of preventing the next human pandemic (deemed as "most likely viral in nature").

Some AI-generated answers suggested that the estimated probability of 60% in the case of the transmissible, potential vaccine candidates could be lower due to a few variations in the created mathematical models applied to epidemiological studies. Nonetheless, a new search was performed using other potentially important scientific arguments, to ensure that a thorough assessment of both transmission and ability of the "domesticated" pathogenic variants to create pandemic conditions was performed, and following such an assessment, DeepSearch AI has returned the same initial theoretical probability of 60%. If AI-generated mathematical models return lower probabilities, there may ultimately be even a final probability of effective pandemic prevention, especially in the long-run, as multiple pandemics may be prevented over the next several decades, given that a wider transmission of such "domesticated", recombinant pathogenic variants would result in a faster production of a herd immunity effect without the causation of pathophysiology at any macroscopic or microscopic level within the host organism. The present situation could be explained by the fact that the attenuated pathogens that became transmissible "factories" for key immune proteins would still induce considerable immunogenic activations that would cross the threshold level of human-to-human transmission, whilst not causing pathophysiology at any such macroscopic or microscopic levels, which was proven to be possible with the widespread occurrence of asymptomatic COVID-19 disease during the SARS-CoV-2-induced pandemic of 2020-2022, though such a candidate approach would specifically ensure that there would be no "silent" clinical signs causative of tissue-related

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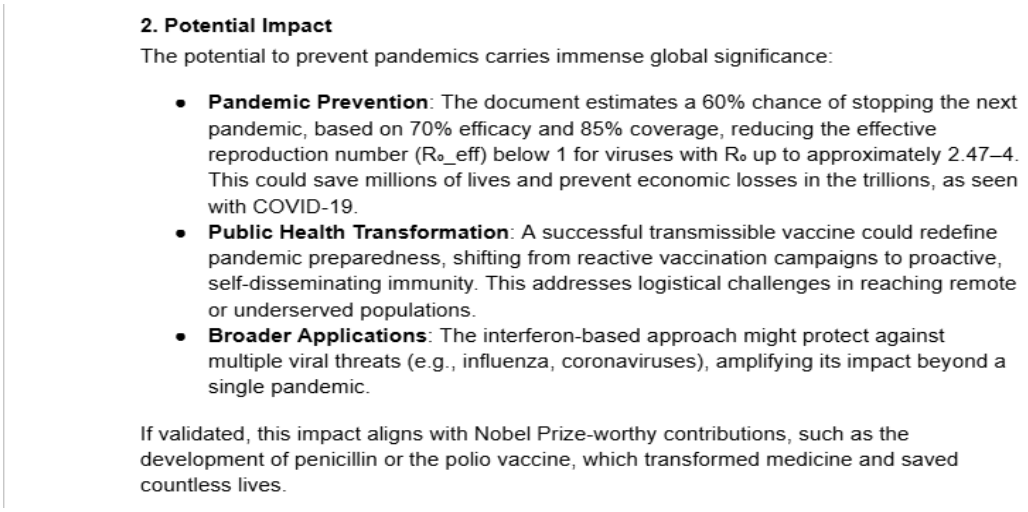
harm detected, in contrast with many asymptomatic forms of COVID-19 disease, which often actually resulted in the onset of clinical disease afterward. At the same time, the AI-generated responses emphasised upon the important need for such a candidate approach to be thoroughly tested to ensure that all guidelines of bioethics and medical safety are respected to the letter, which include the reach of a full state of informed consent throughout the world population, as there are existing theoretical risks that harm will be produced in the process, which the scientific and medical communities must avoid under any circumstances.



2. Potential Impact

The potential to prevent pandemics carries immense global significance:

- **Pandemic Prevention**: The document estimates a 60% chance of stopping the next pandemic, based on 70% efficacy and 85% coverage, reducing the effective reproduction number (R_o_eff) below 1 for viruses with R_o up to approximately 2.47–4. This could save millions of lives and prevent economic losses in the trillions, as seen with COVID-19.
- **Public Health Transformation**: A successful transmissible vaccine could redefine pandemic preparedness, shifting from reactive vaccination campaigns to proactive, self-disseminating immunity. This addresses logistical challenges in reaching remote or underserved populations.
- **Broader Applications**: The interferon-based approach might protect against multiple viral threats (e.g., influenza, coronaviruses), amplifying its impact beyond a single pandemic.

If validated, this impact aligns with Nobel Prize-worthy contributions, such as the development of penicillin or the polio vaccine, which transformed medicine and saved countless lives.

Figure 3. Grok 3 beta (DeepSearch) AI-generated answer regarding potential pandemic prevention effects of such updated vaccine-based methodologies.

The presented novel candidate model of human and animal vaccinology may ultimately demonstrate to contain major traits of a “Revolutionary” approach in vaccine development, potentially covering widespread areas of pathogenic microbiology, as well as epidemiology and immunology that may include wide parts of the animal and plant kingdoms as well. It may be important to emphasise upon the objective of such candidate updates in vaccinology, to effectively create an evolutionary trap for pathogenic microbes, by utilising the principle of “successful conquest from within”, at the genetic level, and not to develop transmissible vaccines by solely using genetic attenuation of microbes, as this alone would not be sufficient to create a useful method of anti-pathogenic evolutionary counteraction and risks would likely outweigh the benefits on the long run. The candidate approach that includes the CRISPR-Cas9-based microbial gene editing step would represent the next level of recombining pathogens for the purpose of vaccine development, as the initial stage was the recombination of surface-level proteins, which would represent a potential predecessor step to the recombination of pathogens at their core, genetic level, in vaccine development. In short, the attenuation of microbial genes responsible for inducing virulence, and the insertion of human genes responsible for the production of the very key immune proteins that the wild-type variants of such microbes directly and indirectly antagonise, would cause the microbial profiles to undergo a mechanism of “self-sabotaging”, which could be described as a “genetic autoimmunity within the microbes”, and altogether, this could lead to their natural de-selection. Overall, the focus of current trends in biomedical and clinical research could lead to major, unimagined breakthroughs of discovery and innovation, particularly if Artificial Intelligence-based research catalysis is utilised correctly, in full accordance with the standards of bioethics, and if all necessary steps of clinical testing are followed accurately. Any “promise” of breakthrough should most likely not be taken too seriously until the threshold level of conclusive evidence, which is collected via thorough clinical studies and accurate real-world data analysis and interpretation (DAI), given the complex nature of scientific validation processes, which contain such a nature as a result of

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the high and multi-lateral extent of uncertain factors that exist around scientific hypotheses, as well as collected preliminary data.

Conclusion

The evolutionary battle between human and animal immune systems and polymorphic pathogenic agents has reached a critical stage, with the current existence of highly profound and firm microbial networks that are evasive of first-line and second-line, natural immunity. It seems that the development of recent epidemic and pandemic diseases has heavily depended upon such evolutionary capabilities of direct and indirect molecular self-camouflaging of the causative pathogens in front of the host interferon system. The fact that there are existing therapeutic approaches designed to target microbial gene products directly or indirectly responsible for the suppression of the host interferon system displays an existing level of scientific awareness to the existing phenomenon of natural immune evasion by numerous microbes. According to the latest stages of scientific, pharmaceutical and clinical research of the human immunity and microbial evolution, there is a paradoxical existence of both unprecedented threats to the integrity of human and animal public health, as well as of novel horizons of hope, as there is a possibility for clinical researchers in almost any geographical area of the world to turn threatening pathogenic agents into immunising factories for foundational, innate immune signals that will automatically activate the adaptive immune system in a manner that is proportionate to the microbial count or load. An update of the current course of therapeutic and vaccine-based research and innovation may likewise involve a proportional inclusion of first-line and perhaps also second-line, natural immunity, to merge a considerable extent of such immune departments with the central, adaptive immune elements, with the overall purpose of naturally stimulating the human immune system to outcompete the highly developed interferon-suppressive evolutionary responses developed by polymorphic microbial agents through numerous rounds of single-nucleotide polymorphism (SNP) in diverse important genes. Such an approach may illustrate the concept of “United Immune System” put in clinical practice. Loss-of-function microbial research may represent a controversial form of research if it is not accompanied by viable methods to turn microbial agents into immunising agents whilst causing no harm in the process, and gene editing via the insertion of active Type I, Type III and perhaps Type IV Interferon-encoding genes may represent the accompanying factor that may turn such a research procedure into a thoroughly ethical one for both the medical and the biological domains. And the current context of advanced microbial evolution may be causing the production of sentiments of urgency within major research communities regarding the development of innovative solutions to proportionately counteract such microbial genetic “intelligence”. Utilising a set of combined approaches, particularly in groups of patients where prophylactic immune support is needed more, may bring the utmost effect of immunisation and long-term immunity. The ultimate objective of such hypothesised and proposed updates in the known methods of immunisation, prophylaxis and early therapeutic approaches is to at least gradually decrease the probabilities of occurring limitations toward the point of zero. DeepSearch AI-derived methodologies were utilised to check the arguments presented throughout the paper, and affirmative results regarding a significant probability of success were generated through the development of mathematical models applied into epidemiological and public health-related studies, using immunological and microbiological arguments and overall mentioning up to 80 peer-reviewed scientific papers as relevant references. Importantly, the metaphor of the eye of the hurricane provides a multidimensional framework—scientific, philosophical, and strategic—for guiding the next generation of immunological interventions. It invites us to reimagine pathogenesis not as a one-sided assault, but as a co-evolving dynamic that can be redirected from within. As climate engineers look to calm storms with aerial technology, so too might biomedicine learn to pacify the microbial storm by mastering its eye. Albeit having a strong potential to effectively change the nature of public health-related and pandemic prevention strategies, potentially even bringing a scientific and medical “Revolution”, it is necessary for the scientific communities to utilise the utmost rigour of clinical testing to ensure that risks do not cross

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any established threshold level, that the ultimate principle of "First, do no harm." established by the founder of medicine is respected throughout the entire process and that informed consent is fully reached as well. Currently, it is the responsibility of the scientific communities to assess and distribute any existing piece of scientific evidence that is relevant to such hypotheses and novel developments into clinical research, with the ultimate purpose of encouraging clinical researchers to assess novel candidate approaches that cross the initial threshold levels of safety and efficacy that are necessary for initial clinical trials to occur.

Author's Note: The present manuscript has been, in part, refined using the 4.0 model of ChatGPT Artificial Intelligence to ensure optimal organisation of the important scientific ideas, hypotheses and points of discussion in the overall process of literature review and exploration of relevant theories and potentially major applied points of philosophy in immunology and vaccine development.

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