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RESEARCH ARTICLE

Adopting Natural Host Immune Response Against Zoonosis

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Abstract

Zoonosis originated from the transmission of pathogens between species. Rapid mutation causes the pathogens to develop resistance to treatments. Thus, there is an urgent need for medications that could maintain efficacy when encountering new strains. This study aims to discern the possibility of overcoming threats from EIDs by recreating immune responses of natural hosts and reinforcing them in the human system. The methodology used is literature study, as the resarcher utilized data presented by similar studies. References will be taken from clinical trials and studies on related topics from PubMed, ResearchGate, and NCBI. Within multiple research papers, it was found that several experts support the idea of mimicking hosts' immunity through the use of interferon. Treatments with IFN-2b significantly reduce viral infection of SARS-CoV-2 in the upper respiratory tract and increase blood levels of inflammatory markers, according to research conducted in Wuhan.Similar results apply in other trials, proving that interferon managed to contain the invasion of pathogens. This is shown through a reduction in the severity of infections, the duration of viral clearance, and levels of mortality. The results conclude that the use of interferon benefits the patient's recovery progress by mimicking the natural host's immune response and heightening the viral clearance rate. More research needs to be done to explore the effect of excessive IFN-α/β usage on immunity.

KEYWORDS:
zoonosis, EIDs, interferons, cytokine, SARS-CoV-2

1 | INTRODUCTION

Zoonotic diseases have become very prevalent in the last 20 years, starting with the severe acute respiratory syndrome (SARS) outbreak in China, the Middle East respiratory syndrome (MERS), and the current coronavirus disease (COVID) pandemic. As humanity realizes the threat of zoonotic diseases looming over us, experts trace back the origin of these diseases. During the SARS-CoV-2 investigation, 85.5–96.2% of overall genome sequence identity in pangolins and bats was found to be related to SARS-CoV-2 (Xiao et al., 2020). Although the official cause of the disease has not yet been announced, based on the transmission of SARS-CoV and MERS, it is evident that this is another case of spillover transmission across species. Through phylogenetic analysis, the SARS coronavirus (SCoV) was identified as the direct ancestor of the SLCoV outbreak in 2003. The SCoV lineage was discovered to have undergone interspecies transfer between reservoir hosts and bats to amplifying hosts, which are Paguma larvata and Nyctereutes procyonoides, around 4.08 years before the outbreak (Hon et al., 2007). It is only a matter of time before drug developments are unable to cope with the rapid progression of emerging new zoonotic diseases or variants.

Several research groups have conducted experimentation on altering mechanisms of human immunity to mimic those of the reservoir's hosts. Yet, there are no certainties as to what degree or efficacy these treatments could affect viral replication and promote viral clearance in humans. In this study, the researchers explore whether the use of IFN in treatments would have a significant impact on the recovery process. They utilized comparative studies on the results of leading clinical trials to illustrate the potential of IFN treatments against the deadly and contagious SARS-CoV-2.

It is estimated that 58% to 61% of all communicable diseases worldwide fall under zoonotic diseases (Woolhouse Gowtage-Sequira, 2005; Taylor, Latham Woolhouse, 2001). That percentile also represents 75% of the EIDs that have infected numerous people over the past decade. Cases of zoonotic transmission range from exposure to wild or domesticated animals and products of animal origin (Woolhouse Gowtage-Sequira, 2005; Jones et al., 2008).

The COVID-19 pandemic illustrates the scale of impact that EIDs would have in the current world. The inability of medical technology to accommodate the violent viral progression caused over 70 000 people to be infected and 1800 deaths in the first 50 days of the pandemic (WHO, 2020; Knight, 2020). SARS-CoV-2 is more contagious but less deadly than its ancestor strain, SARS-CoV (2003). SARS-CoV managed to infect 8098 people, with a mortality rate of 9% across 26 countries. In contrast, there are 120 000 individuals infected with SARS-CoV-2 and a reduced mortality rate of 2.9% across 109 countries (Shereen, Khan, Kazmi, Bashir Siddique, 2020). Although the percentile seems small, the virus has managed to eliminate 4,830,367 individuals, 2% of the infected population (Meter, 2021).

Zoonotic transmission could come in various forms and mostly depends on the pathogen discussed. Generally, the first human infection of zoonotic pathogens is transmitted through vector-borne pathways, direct animal contact, airborne pathways, oral transmission, and exposure to the contaminated environment as show in Figure 1 (Loh et al., 2015). Pathogen transmissibility is determined by structural features such as virus particle size, genome segmentation, and the presence of lipid envelop, as well as reservoir hosts (Walker, Han, Ott, Drake, 2018).

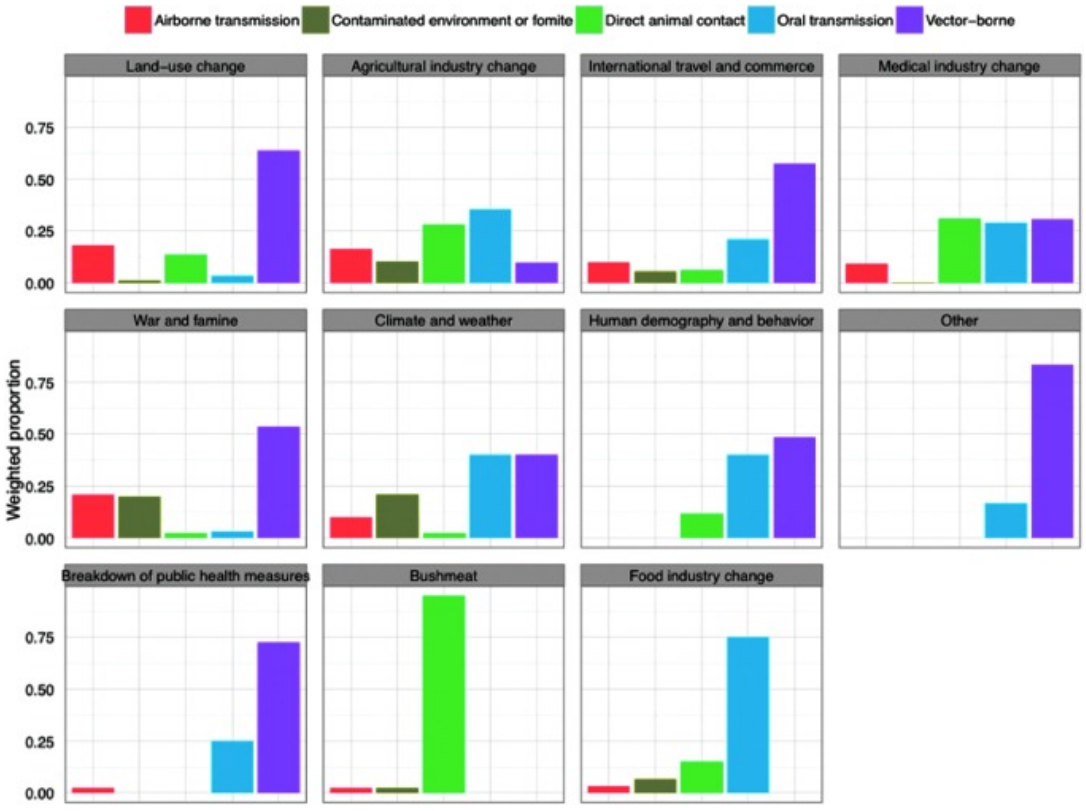

FIGURE 1 Distribution of zoonosis diseases cases in respective transmission pathways (Loh et al, 2015.))

The key to sustainable recovery is immune balance, indicating the need for drugs and medications to regulate and prevent excessive stimulation. With similar cytokine complexes secreted during the first infection by both hosts, medications inspired

by the reservoir's immune mechanism would most likely have a higher efficacy. Examples of these drugs are synthesized inflammatory inhibitors and PEG IFN2 (Pandit et al., 2021).

2 | METHOD

A collection of research articles has been published on zoonotic diseases and host animals' immune responses to such pathogens. The majority of attention has been focused on interferon release during the innate immune response, but IFN- treatment may produce positive results. Literature research was chosen due to the abundance of new research papers on COVID-19, zoonotic diseases, and the human immune system in the past few years. A new perspective to look at the development of cures for zoonotic diseases is necessary as the development would tend towards modifying humans' innate immune systems to be as mild as possible when facing an infection, thus copying the reservoir host. As no rigorous research papers have been published on evaluating the collective results of this research, this is a good opportunity to discuss the viability of such methods to help the human body adapt to new diseases. In the papers chosen, qualitative evidence is adopted as proof that the symptoms of zoonotic diseases may be treated by means of forcing an immune response similar to that of the original hosts. Multiple pieces of evidence show that humans can have adaptive immune responses without causing potentially fatal side effects like cytokine storms (Abdolvahab et al., 2021). By understanding how these immune responses in zoonotic disease occur, a way to implement this into medical practice may thus be formulated, given that the process is safe for humans. So far, multiple researchers have been supportive of this idea, although primary research is needed in order to obtain quantitative data on the effective efficacy of this treatment compared to current widespread treatment (Darazam et al., 2021; Zhou et al., 2020).

3 | RESULTS AND DISCUSSION

3.1 | Mutagenic nature of zoonosis virus

The severity of viral infections can be forecasted by the amount of cross-transmission undergone by the virus. The virus is unable to adapt or remain "alive-on-arrival" during zoonosis due to difficulties in accurately interacting with host proteins in a new species (Warren Sawyer, 2019). This is caused by differences in the primary sequences of these proteins from cells in natural hosts. This leads to the viral interaction surfaces being modified. Every modification within the protein coat of the virus indicates that the virus has undergone either viral mutation or recombination for adaptive features. This explains the rapid rate of strains emerging from viruses such as EbolaV and SARS-CoV-2. Mutations are known to be a stimulated process, caused by agents such as physical mutagens (UV light, x-rays) targeting nucleic acids, the nature of the bases, and the fallibility of the enzymes in the replication of DNA. In fact, mutations in human cells are prevalent and undergo the same stages as viruses. However, the rate of mutation, particularly in RNA viruses, is significantly high because of the lack of "proofreading" functions in their replicative enzymes (Fleischmann, 1996). This also reinforced the fact that most viral diseases that managed to cross over species were identified as RNA viruses (Mandl, Schneider, Schneider Baker, 2018).

According to research on behavioral differences between viral strains, the G614 virus, a variant of SARS-CoV-2 D614, projected higher infectious titres and amplified viral replication than the D614 virus in nasal washes and tracheas, but there are no differences in patients' weight loss or other symptoms (Plante et al., 2021). Despite only a few strains persisting to be a part of virus populations, any form of change in nucleic acids could significantly impact the progress and behaviour of the virus.

Several studies have also shown that mutation products have mechanisms that directly attack the innate immune response, with several strains specifically blocking induction or infecting novel host interferon responses, limiting innate immune signaling pathways.Ebola Virus VP35 and VP24, influenza virus NS1, SARS CoV NSP1, and ORF3b are just a few examples (Ayllon García-Sastre, 2014). Interception of ISGs, other immune recognition pathways, restriction factors, or production of effector molecules are common traits in mutated strains (Menachery et al., 2014). These demonstrate that viral strategies in invading the immunity of novel hosts are detrimental in ascertaining the efficacy of the immune response (Mandl et al., 2015).

3.2 | Human Immune Response

Diverse zoonotic pathogens contracted by humans can be differentiated by their definite manifestation in biological and clinical form, yet most of them evoke several immunopathological components after their incubation period ends (Mandl et al.,

2015). These infection outcomes may vary in the degree of severity of symptoms and the duration of progressivity, such as pneumonia with hypoxemia or acute respiratory distress syndrome (ARDS) with severe and critical symptoms (Yuki, Fujiogi Koutsogiannaki, 2020).

The start of a human immune response begins with the detection of antigens discharged from the virus by innate immune effectors. Other cells of the immune system, such as T-cells and B-cells, will release specific cytokines, chemokines, and lipid mediators in response to the stimuli. Furthermore, this sets "downstream adaptive responses that themselves can modulate the innate response." Maintaining the balance between exuberant responses that eradicate viruses through poisoning infected organ cells and responses that restrict the effects of immunopathology (Cameron, Bermejo-Martin, Danesh, Muller Kelvin, 2008; Kuiken, Riteau, Fouchier Rimmelzwaan, 2012). It is critical that the body achieve equilibrium between protective and pathogenic immune responses to support the effective eradication of pathogens and recovery.

Among several chemicals released during the innate immunity response, interferons are described as an agent preventing viral replication in body cells. IFN- and IFN-, stimulates expression of MHC class I molecules on infected cells and development of Th1 cells, along with natural killer (NK) cells apoptotic and lysing activities. IFN- and IFN- originated from common ancestors, unlike IFN-gamma, which is "immunity induced" (Ferreira, Borba, Bonetti, Leonart Pontarolo, 2018; Alberts et al., 2002). The production of IFN- depends on the infected leukocyte virus, while IFN- is from fibroblasts infected with the virus (Rouse Sehrawat, 2010).

However, innate immunity could bring potential dangers to patients as it is displayed in cytokine storm cases in the majority of COVID-19 patients. The explanation behind these self-destructive attacks similar to autoimmune diseases is over-stimulation of endosomal TLRs (TLR3, TLR7, TLR8, and TLR9), RIG-I, and NLRs. With many receptors activated, it induces pro-inflammatory cytokines and IFNs to be produced, and signals activated cells or recruit innate inflammatory cells involved in inflammation and the induction of adaptive immunity (Rouse Sehrawat, 2010). Furthermore, excessive activation leads to local tissue damage and reduced efficacy of protective adaptive immune responses (Kash et al., 2006; Peiris, Cheung, Leung Nicholls, 2009). The degree of inflammation would depend on the progression of viral activity. Several virus strains, such as H5N1 and the 1918 H1N1, stimulate activation of high-level sustained proinflammatory cytokine production following infection (Kash et al., 2006; Peiris, Cheung, Leung Nicholls, 2009). The effectiveness of the host response to infection is dependent on the interaction of innate and adaptive immune responses, viral strategies for immune evasion, and the deleterious consequences of hyper-activated or misdirected immune responses (Mandl et al., 2015).

There is still restricted research done in exploring further the vitality of the inflammasome pathway. Investigation into the pathways of the inflammasome is necessary to identify reasons behind the severity of damage done by humans' innate immune system in most zoonotic infections. When the body identifies pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), it activates downstream inflammatory pathways (Kelley, Jeltema, Duan He, 2019). The production of inflammatory cytokines is heavily regulated by inflammatory caspases-1, -4, and-5. When these caspases are activated by inflammasomes, the pathway will divert into canonical and noncanonical. They are differentiated by the different cytosolic PRRs from the NLR (nucleotide-binding domain leucine-rich repeat) (Groslambert Py, 2018).

Generally, the objective of inflammatory responses is to reinforce a conducive healing environment through which cellular and molecular reactions are shifted to minimize the spread of acute injury or infections (Zhou, Hong Huang, 2016). At different anatomical levels, inflammation can be presented in different forms, such as in tissues where it is depicted as redness, swelling, loss of function, and discomfort. However, at the micro-level, inflammation controls vascular permeability, accumulation and recruitment of leukocytes, and inflammatory mediator release (Ferrero-Miliani, Nielsen, Andersen Girardin, 2007).

However, the exuberant release of inflammatory cytokines will lead to tissue damage, hemodynamic changes, organ failure, and increased mortality (Czaja, 2014; Liu, 2016). The failure in maintaining the homeostasis of inflammation occurs when acute inflammatory mechanisms are unable to eliminate tissue injury (Lintermans, Stegeman, Heeringa Abdulahad, 2014).

The high prevalence of dysregulation of innate immunity in COVID-19 and Ebola, which resulted in organ complications progressing ultimately to death, illustrates the strong correlations between zoonotic diseases and the hyperactivation of the immune response. SARS-CoV-2 infection restricts cellular immunity by reducing the levels of activated T cell markers and lymphopenia. Late activation markers such as CD25 and PD-1 in both CD4+ and CD8+ T cells are enhanced, and proinflammatory cytokines are released, which leads to cytokine storm (Yang et al., 2020).

Cytophenia, hyperferritnemia, and elevated IL-6 levels are all common triggers for cytokine storm syndrome (CSS) and secondary hemophagocytic lymphohistiocytosis (sHLH) (Mehta et al., 2020; Moore June, 2020) rate of patients contracting CSS syndrome could be lowered if early identification and treatments were used to restrict the rampant release of IL-6 and other pro-inflammatory cytokines (Melo et al., 2021).

3.3 | Natural Host's Immune Response

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3.4 | Natural Host's Immune Response

The transformations in the dormancy of pathogens during a spillover from hosts to non-natural hosts are caused by differences in the mechanism of the within-host immunopathological process and the novel response (Mandl et al., 2015). Host immune response is fundamental to understanding the interrelationship between reservoir host and virus and is utilized to forecast the development of the virus in a new organism and the degree of contagiousness. Several observations have been reported on the severity of symptoms present in simian immunodeficiency virus of chimpanzees (SIV cpz), the viral ancestor of HIV-1, in African green monkeys and sooty mangabeys, the viral natural hosts (Keele, 2009; Pandrea Apetrei, 2010; Silvestri et al., 2003). The results show that there are no detectable side-effects on health or survival in the organisms, despite the high-level of prevalent cases and viral replication.

Recent studies revealed natural hosts are able to asymptomatically carry zoonotic pathogens because of their dampened innate immune pathways, which do not form effective barriers or responses to prevent viral infection. This allows viruses to easily establish stable infections inside the host without stimulating apoptosis or inflammation (Letko, Seifert, Olival, Plowright Munster, 2020).

Virus-host equilibria are established successfully if the reservoir hosts do not contract any alarming health concerns from the infection. By then, zoonotic pathogens were able to invade the natural host's body without detection for a significant duration of time (Mandl et al., 2015). The mechanism of disease tolerance should retain pathogen specificity to some degree in maintaining immunocompetence (Schneider Ayres, 2008).

External factors, such as viral tropism, can influence pathogenesis development at the host-virus interface. This applies to the cases of sooty mangabey and African green monkeys. Sooty Mangabey retains memory T cells with reduced CCR5 expression (a coreceptor for SIV) that are resistant to infection (Paiardini Müller-Trutwin, 2013). Likewise, African green monkey memory T cells with CD4+ demodulate CD4 expression, restricting dysregulation of their homeostasis and increasing resistance to SIV infection (Beaumier et al., 2009). Several studies support the idea that the microbiome contributes to the role of modifying the hosts' response to viral infections (Virgin, 2014). This is reinforced by the fact that innate immunity activation thresholds are determined based on their previous exposure to pathogens (Mandl et al., 2015).

Bats are regarded as one of the ideal reservoir hosts for 60% of the discovered zoonotic pathogens, with the majority of them identified as RNA viruses (Streicker et al., 2010; Fisher, Streicker Schnell, 2018; Zhang et al., 2013), such as EbolaV, SARS-CoV-2, and others. Therefore, the researchers decided to adopt bats' immunopathological responses as the main model to represent other natural hosts. Comparison between human and bat physiological factors such as the ability to fly proved to have a secondary effect on the immunity of the organism, namely that they possess an assortment of DNA damage checkpoint pathways which overlap with the determination of the innate immune system (Irving, Ahn, Goh, Anderson Wang, 2021). Several experts hypothesized that the innate immune mechanism of bats was derived from pathogen exposure history and selective adaptations that alternated the immune signaling pathways (Mandl, Schneider, Schneider, Baker, 2018). This idea is further supported by the abundant concentration of selected genes in the DNA-damage checkpoint pathways important for cell death, ageing and innate immune pathways (Irving, Ahn, Goh, Anderson Wang, 2021).

The comparative study of the bats' genomes confirms that the organisms possessed a specialized pathway, PAMPS, within their innate response mechanism. In addition, the organisms are able to produce IFN-1, T cell and B cell responses (Baker, Schountz Wang, 2012). Furthermore, there is a lack of PYHIN expression in genes across 10 bat species. PYHIN encodes DNA sensors that detect foreign DNA and damaged self-DNA and sensors that stimulate the production of proinflammatory cytokines. Without this gene, the innate immune response would be slowed down, as IFN cannot be produced due to low stimulation within the stimulator of interferon genes (STING) and the innate response is collectively restricted from dysregulating (Li et al., 2015; Darazam, 2021; Ahn, Cui, Irving Wang, 2016; Iwasaki, 2012). STING is an integral pattern recognition receptor that conciliates cytosolic-DNA-induced signaling and has a major role in infection, inflammation, and cancer (Barber, 2015). Despite the outcomes, it is important to remember that the absence of gene expression does not limit the probability of involvement of other proteins to repress the defect.

Experimental infections were done on several species of bats to further test the immunopathological response after exposure. In this study, low levels of antibodies were detected in all bats, with the exception of P.poliocephalus, which developed a significant neutralizing antibody titre, possibly because the organism is not a natural host for the administered virus (Middleton et al., 2007).

Protein apolipoprotein B mRNA editing enzyme and catalytic polypeptide-like (APOBECs) were discovered in a bat species, Pteropus alecto (Hayward et al., 2018). Currently, only this species has been identified to possess this protein. APOBECs stimulate deamination of DNA cytosine residues, resulting in hypermutation of the nascent retroviral DNA, thus rendering them non-functional (Narvaiza et al., 2009). The production of APOBECs is induced by the presence of a small amount of IFN type 1 present in the blood (Mohanram, Sköld, Bächle, Pathak Spetz, 2013). This explains the effective mechanism of immunopathological response in bats without inflammasome production.

Observation of the in vitro innate immune response of Pteropus alecto suggests that rather than blindly dampening their first line of defence, bats steadily increased their IFN excretion. IFNs discovered in the systems are type 1 (IFN- and IFN-) and IFNL (III). In humans and mice, IFNL was shown to perform several regenerative activities such as diminish neutrophil functions and modulating tissue-damaging, along with transcription-independent responses (Cameron, Bermejo-Martin, Danesh, Muller Kelvin, 2008; Zanoni, Granucci Broggi, 2017). Pteropid bats have their own constitutive expression of mRNA for IFNA and IFN regulatory factor 7 (IRF7) in unstimulated tissues and cells (Zhou et al., 2014). This unique trait may be the reason behind their agile response towards pathogens and the decrement in the lag time, which causes adverse symptoms in humans, such as cytokine storms.

A mathematical model shown in Figure 2 predicts a comparative study between the degree of severity caused by inoculum between humans and bats. This is done to identify the efficacy of innate immunity in each organism by assessing the inflammasome activity in each mechanism (Cockrell An, 2021).

The Y-axis labelled as End-State%System-Health represents the degree of damage done to the organism, and the X-axis labelled as Rank-Ordered Population Distribution reflects the “stochastic replicates” ranked by their health conditions by the end of the simulation.

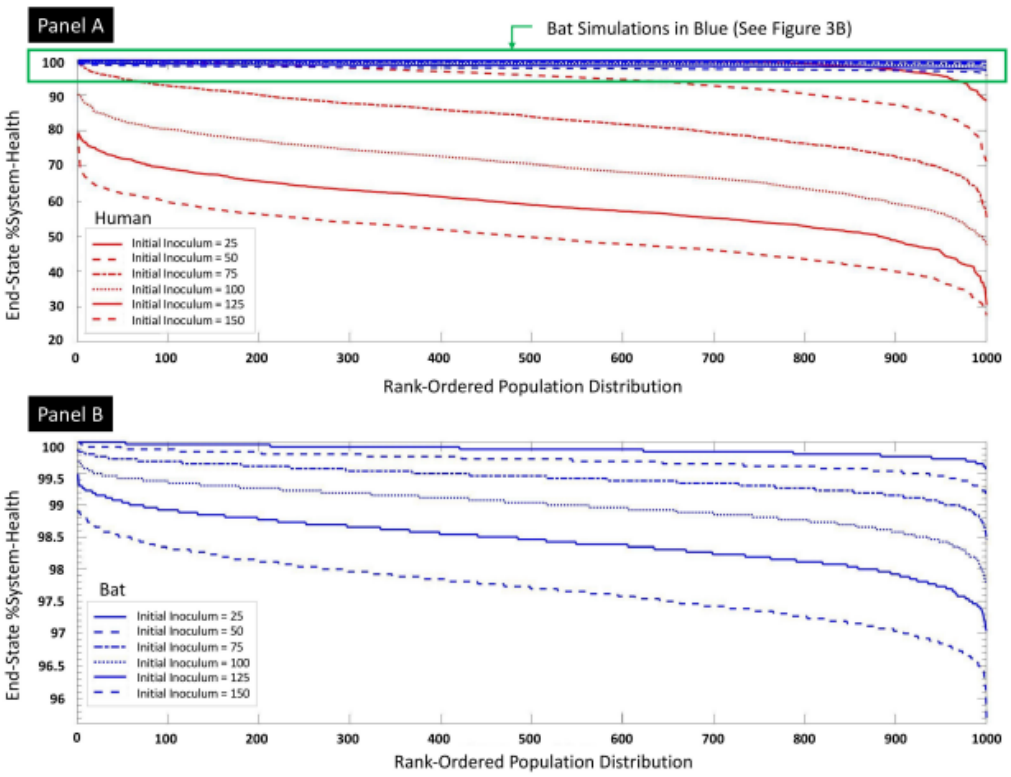

FIGURE 2 Comparison in Bats and Humans severity of innate immune response effects on the body (Cockrell An, 2021).

The curve reveals that an increased level of inoculation would increase the progression of dysregulation of innate immunity. Additionally, Panel A confirms that within the parameterization, bats are unaffected by the disease. On the contrary, as the experiment advances, the end-state system health of humans deteriorates rapidly. Panel B represents the magnified bats' parameterization, confirming that the results still follow the trend of dose-dependency.

3.5 | Adoption of reservoirs innate immunity

IFN treatments are not a foreign concept in the field, as various IFNs are already commercially utilized to aid in rehabilitating viral diseases such as Hepatitis B and C. The mechanisms of IFN vary according to the virus dealt with; this is caused by differences in the IFN antagonists present. Nonetheless, to the best of our knowledge, there have been numerous cases in which a virus has developed complete resistance to IFN and thrives in replication.

There are several attempts to administer IFN type 1 daily to reinforce the early response of innate immunity. These experiments are done under the assumption that a particular IFN can universally inhibit the viral replication of viruses in the same family. This is proven to be true in the case of pegylated interferon alfa-2b in the treatment of COVID-19. This IFN was previously used as a MERS-CoV cure. IFN 2b has a covalent conjugate of recombinant commonly referred to as PEG IFN-2b (Pandit et al., 2021). The JAK/STAT pathway is stimulated by the presence of a compound that increases gene expression in innate immune system tissues (Dandekar Perlman, 2005).

In 2020, there were two major clinical trials implementing IFN treatment on COVID-19. The Lokugamage and Zhou experiments paved the trend of adopting early interferon treatments in COVID-19. The research confirmed that SARS-CoV-2 maintains similar viral replication to SARS-CoV, with 80% identical nucleotide identity. In addition, SARS-CoV-2 has been proven to be more sensitive to IFN-I. One of the attempts utilized Vero cells pretreated with IFN-I prior to the infection as a medium. SARS-CoV infections are slightly reduced in viral titer of 1.5 log10 plaque-forming units (PFU) compared to untreated 24 hours' post-infection. By 48 hours, SARS-CoV viral yields are equal to those in untreated conditions. Contrastingly, SARS-CoV-2 viral replications are significantly reduced in mediums with IFN-I treatment. In 24 and 48 hours of post-infection, SARS-CoV-2 infections are 3-log10 (24 HPI) and 4-log10 (48 HPI) drops in viral titer compared to the control. This explains the high efficacy of IFN treatments on infected patients, shown through the remarkable difference in viral activity that creates a conducive environment for recovery (Lokugamage et al., 2020).

However, there are already several chemical and physiological adaptations from the virus to achieve IFN resistance. Several examples of IFN's antagonists are ORF1ab poly-protein and ORF3b, a 154 amino acid complex that restricts IRF3 phosphorylation (Kopecky-Bromberg, Martínez-Sobrido, Frieman, Baric, Palese, 2007). Figure 3 shows the effects of different IFN administration on viral titre.

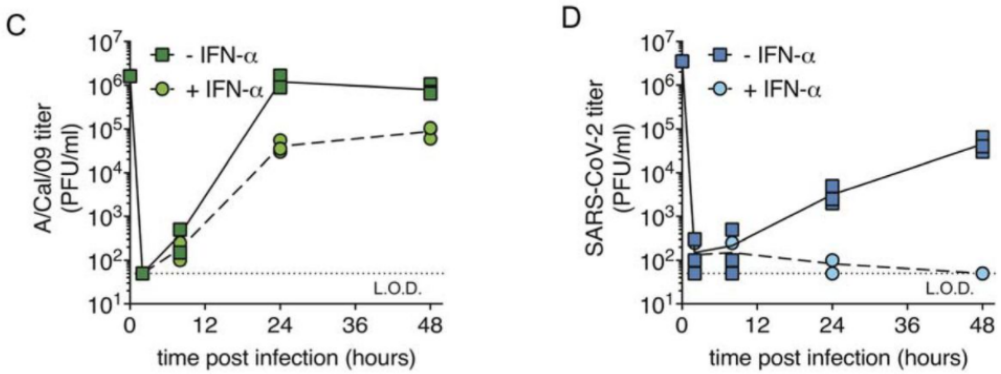

FIGURE 3 Effects of different IFN administration on viral titre (Darazam, 2021).

The Zhou experiment as shown in Figure 4 was carried out in the epicentre of the pandemic, Wuhan. Seventy seven (77) patients are administered different medications, which are IFN, ARB, or IFN+ARB. Among 50% of the subjects, treatment started within 72 h of the positive PCR result and 25% started between 72 h -96 h while the other 20% started within 10 days after the confirmation of infection. Average days of viral clearance were achieved within 27.9 for ARB-only medication, 21.1

days when treated only with IFN-alone, and 20.3 days for patients administered with the combination of both. This confirms that IFN-2b treatments accelerate viral clearance within the body (Zhou et al., 2020). The duration of treatment commencement between confirmation of PCR (+) is considered an integral factor in determining the viral shedding, clearance, and mortality rate of the patient (Pandit et al., 2021).

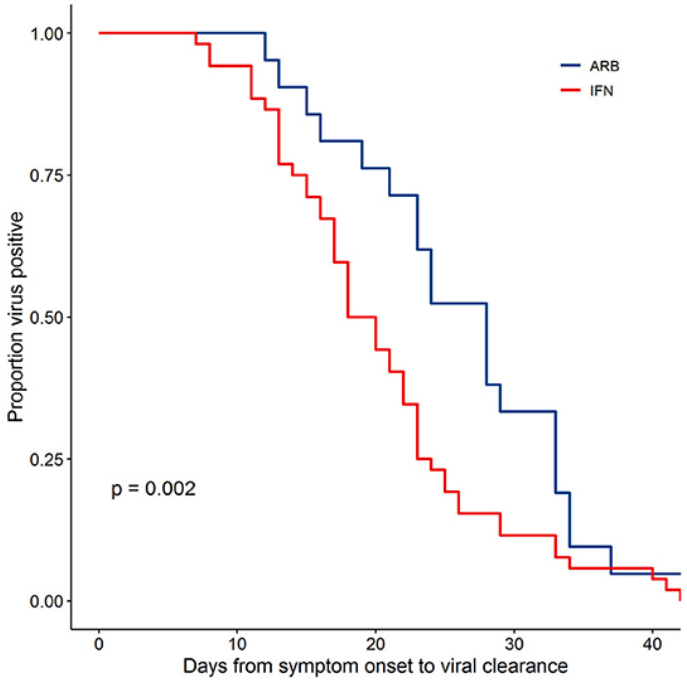

FIGURE 4 Viral clearance progression during administration of ARB and IFN (Zhou et al, 2020).

Inflammatory cytokines IL-6 and CRP are reduced when IFN is administered into the patients, while ARB dependent drug stimulates a contrasting result in which the levels become significantly elevated, as illustrated in Fig 5. However, these treatments did not affect other inflammatory cytokines within the experiment (Zhou et al., 2020).

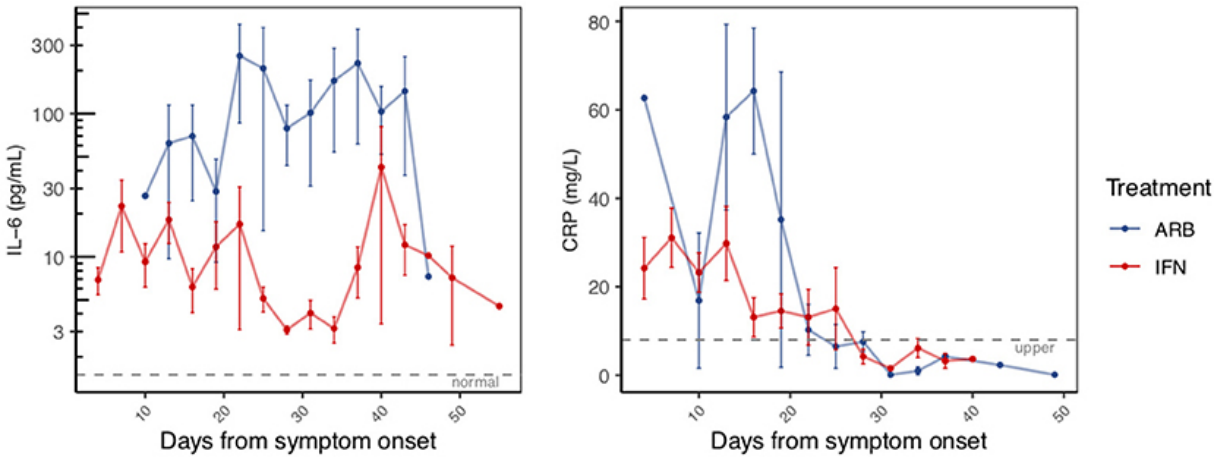

FIGURE 5 Concentration of IL-6 and CRP cytokines after ARB and IFN treatments (Zhou et al, 2020).

Within the trial, the patients are still administered with antipyretics, cough suppressants, antibiotics, steroids, vitamins, anticoagulants, and hydroxychloroquine according to the protocols published by WHO (Pandit et al, 2021). Thus, IFN administration did not act independently and may be affected by the presence of other drugs in the system.

4 | CONCLUSION

Collectively, the results confirm that IFN treatment can facilitate a sustainable recovery against zoonotic pathogens. This is mainly caused by the instantaneous response of an appropriate level of innate immunity and the allowance of human intervention in controlling the immunopathological feedback. With constant regulation of the cytokine compounds, the researchers establish virus-host equilibria or periodic viral shedding. Hence, the chances of hyper-activation or immune dysregulation could be reduced. This prevents a self-destructive phase and increases the prevalence of adverse organ complications.

4.1 | Suggestion

Further research to explore the topic is needed to assist in the formulation of a new treatment plan utilizing IFN and inhibitors to sustain the innate immunopathological response and prevent hyperactivation. Despite being shown numerous times to be successful in facilitating the rapid recovery rate of infected patients, all of the attempts covered in this research have only ended in short clinical trial stages currently. There are also several risks that viruses may potentially develop IFNs antagonistic traits. However, with the high potential of viral clearance and reduced mortality rate, the benefits of this treatment outweigh the risks. Despite that, further observation should be done to identify potential adverse effects of utilizing the treatment for the long haul.

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