Review of: "A Harmless Avian Vaccine Virus Could Be Developed into an Off-the-Shelf “Antibiotic” for Viruses"

Luca Soraci[1]

1 Unit of Geriatric Medicine, INRCA Istituto Nazionale di Ricovero e Cura per Anziani, Ancona, Italy

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Many thanks for the invitation to revise the present commentary. The article presents an innovative concept of repurposing the infectious bursal disease virus (IBDV) as a broad-spectrum antiviral agent. While the idea is compelling, several critical concerns need to be addressed for this concept to be considered viable in clinical and regulatory settings. These are my major comments that I hope will be helpful for increasing the quality of the paper:

-1. Scientific Justification and Mechanistic Understanding: While the article emphasizes IBDV’s ability to upregulate type I interferon genes as the cornerstone of its antiviral activity, there is insufficient mechanistic detail provided. The reliance on broad assertions like “activating the native antiviral defense system” fails to elucidate the molecular pathways that confer specificity or efficacy against diverse viruses. A clearer explanation of how IBDV selectively interacts with host immune responses without exacerbating inflammation is critical.

2. Evidence from human studies: The evidence provided for the efficacy of IBDV in humans is sparse and largely anecdotal, such as the first author's recovery from herpes zoster ophthalmicus. References to limited studies involving fewer than 50 patients do not provide robust clinical validation. Broader Phase I and II trials, supported by peer-reviewed data, are necessary to substantiate the claims made. The commentary’s reliance on limited studies undermines confidence in the generalizability of the findings.

3. Addressing safety concerns: the article repeatedly asserts the safety of IBDV based on its historical use in poultry and limited human exposure. However, it underestimates the potential risks of zoonotic transmission or unforeseen side effects in humans. The assertion that “IBDV treatment never induced excessive pro-inflammatory cytokines” needs comprehensive data from diverse patient cohorts, particularly those with comorbidities or compromised immune systems. Further, regulatory skepticism surrounding live-virus therapies is acknowledged but not adequately addressed.

4. Practicality of broad-spectrum antivirals: The authors argue that IBDV could serve as a universal antiviral to complement vaccination strategies. However, they do not sufficiently address the challenges of creating a true broad-spectrum antiviral. The effectiveness of IBDV against RNA viruses like influenza and coronaviruses might not extend to DNA viruses or other unrelated viral families without extensive modifications. The commentary should clarify the limitations of such an approach.à

5-Overemphasis on Pandemic Preparedness

While pandemic preparedness is a critical concern, the article focuses disproportionately on this aspect without delving into the immediate utility of IBDV for existing endemic viral infections. A more balanced discussion on how IBDV could address current unmet medical needs alongside pandemic prevention would strengthen the argument.