Reviewer Comments

This review focuses on immunoinformatics software used in recent years for vaccine design, specifically in the context of fish vaccine development. It provides a comprehensive summary of the software and discusses how it is used to design vaccines based on in silico epitopes, develop multi-epitope vaccines, and explore the molecular interactions of immunogenic vaccines. The review examines the practical and effective results of using immunoinformatics to address fish diseases and their frequency. It also predicts immune mechanisms and the application of immunoinformatics in fish diseases using TLR signaling pathways.

1. Please provide more context and background information on the importance of aquaculture in meeting the global demand for fish and the challenges it faces, such as increasing unsustainable fishing practices and the need for disease control.

2. It would be helpful to include specific examples of the economic losses caused by fish disease outbreaks in the aquaculture industry to emphasize the significance of the problem.

3. Please include a statement about the safety and efficacy of fish vaccines in general to address any potential concerns or misconceptions readers may have.

4. Provide more information on the role of immunostimulants and adjuvants in fish vaccines, including their mechanisms of action and specific examples of commonly used substances.

5. When discussing the methods of vaccine administration (injection, immersion, oral), elaborate on the advantages and disadvantages of each method, such as efficacy, practicality, and potential stress on the fish.

6. Include more information on the specific side effects that fish may experience after vaccination and strategies to mitigate these effects.

7. Majority of the B- and T-cell prediction tools were developed and trained using data derived from human and mammalian MHC/HLA alleles. Authors need to explain further how could the tools may address in vaccine design for aquaculture?

8. What is the potential role of immunoinformatics and multi-epitope vaccine design in enhancing vaccine manufacturing capacity in low- and middle-income countries?

9. How can researchers and policymakers support the expansion of collaboration and knowledge exchange in the field of fish vaccine design based on immunoinformatics approach, and what are some promising strategies for achieving this goal?

10. As we are aware there are plenty of immunoinformatics papers published since emergence of COVID-19. However majority of these papers published recently were focusing only on computationally analysis using online tools (without lab-based validation). How do you determine the protective efficacy of the identified vaccine candidates of such papers especially in the area of aquaculture? The redundancy of theoretical vaccine papers could not help much in essential vaccine development. Please comment this in your discussion.