Reviewer 1:

Dear Authors,

The present review article entitled 'Viruses and Autism: A Bi-mutual cause and effect' is a well-written and useful summary of the current status of knowledge on the possible effects of viral infection during the critical development period on the risk of developing autism. Results showed that there is an increased risk of developing autism with a specific viral infection during the early developmental period and an increased risk of viral infections in children with autism, especially for specific viral infections such as Rubella, Cytomegalovirus, Herpes Simplex virus, Influenza virus, Zika virus, and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

In general, I think the idea of this manuscript is really interesting, and the authors' fascinating observations on this timely topic may be of interest to the readers of the World Journal of Virology.

However, some comments, as well as some crucial evidence that should be included to support the author's argumentation, needed to be addressed to improve the quality of the manuscript, its adequacy, and its readability prior to the publication in the present form, in particular reshaping parts of the Introduction and Methods sections by adding more evidence and theoretical constructs.

Please consider the following comments:

1- A graphical abstract that will visually summarize the main findings of the manuscript is highly recommended

Our reply: We added a graphic abstract. Thank you.

2- Abstract: Please present the abstract with 200-220 words, max 250 words and proportionally present the background, the objectives, the short summary, and the conclusion. The background should include the general background (one to two sentences), the specific background (two to three sentences), and the current issue addressed to this special issue (one sentence). The short summary closes with one to two sentences that put this study into a more general context. The conclusion should include one sentence describing the main message of the authors, the potential and the advance this article has provided in the field, and finally, a broader perspective (two to three sentences) readily comprehensible to a scientist in any discipline.

Our reply: We modified the abstract following the reviewer's recommendation. Changes are highlighted in red. Thank you.

Please expand the abbreviation in the first appearance. Also, in my opinion, a lack of explanation of the tight relationship between viral infections and autism spectrum

disorders, specifically on how this may impact genetic and epigenetic causative factors contributing to this neurodevelopmental disorder, makes the reader unable to grasp the key aspects of this paper by consulting the abstract. I suggest reorganizing the abstract, making sure to include an explanation of this concept.

Our reply: We followed the reviewer's instructions. Changes are highlighted in red.

3. PROPOSED UNDERLYING PATHOPHYSIOLOGY OF AUTISM:

This section is well-written and nicely presented. Nevertheless, I believe that more information on the pathophysiology of ASD from a more neuroscientific point of view will provide a better and more accurate background. Considering that this study's main focus is to deepen current understanding of neurobiological (specifically structural abnormalities of the brain) in ASD patients, I suggest the authors to make such effort to provide a brief overview of the pertinent published literature that offer a perspective on social impairments in ASD disorder because as it stands, there is no mention of this in the manuscript. For this reason, I would suggest some relevant evidence that will methodologically fit with the present manuscript: we know that ASD is diagnosed based on behavioral impairments in social communication, fixation in interests and repetitive behaviors (see American Psychiatric Association, 2013). These social impairments may be related to the interpretation of social signals: evidence from healthy individuals suggest that potentially threatening situations, such as others' proximity, can trigger a number of physiological responses that help regulate the distance between themselves and others during social interaction

(https://doi.org/10.1038/s41598-021-82223-2;

DOI: 10.1007/s00702-022-02513-5), showing the critical role of social signal interpretation in social interaction

(https://doi.org/10.1007/s00221-020-058294;
https://doi.org/10.3390/biomedicines10040849).

Individuals with ASD have social impairments, potentially due to the lack of social signal interpretation, and therefore resulting unable to interpret these signals to guide appropriate behaviors.

Our reply: We added a paragraph about these changes. Changes were highlighted in red.

4. The objectives of this study are generally clear and to the point; however, some ambiguous points require clarification or refining. In my opinion, authors should be explicit regarding how they assessed the mutual relationship between autism and

viruses: it would be more informative if they explicitly stated how their research focused on how they focus on how viral infections affect brain development and on how this could be at play in some traits commonly associated with autism, such as difficulty communicating verbally or recognizing familiar faces.

Our reply: The aim of the study was modified according to the reviewer's recommendation. Changes are highlighted in red. Thank you.

5. Specific Viral Infections and the Risk of Developing Autism: I was wondering why the authors did not take into account also the possible effect that maternal infections, like Varicella zoster virus or Plasmodium falciparum, may have on the risk of developing autism disorder?

Our reply:

We do agree with the reviewer that we need to add a varicella zoster. However, Plasmodium falciparum is out of the scope of the review as we are focusing on viral infections.

6. Discussion: In this final section, the authors described the results and their argumentation and captured state-of-the-art well; however, I would have liked to see some views on a way forward. Hence, I ask them to include some thoughtful as well as in-depth considerations, making an effort, trying to explain the theoretical as well as the translational application of their research. In this regard, I believe that it could be useful to further investigate the neurobiology of ASD, specifically exploring how the mechanism of inflammatory transformation of specific cell types could be the basis of the early onset of brain developmental defects associated with ASD (https://doi.org/10.3390/cells11162607 ; https://doi.org/10.3390/biomedicines9050517), also affecting cognitive functions (https://doi.org/10.3389/fnbeh.2022.946263 ; https://doi.org/10.3389/fnbeh.2022.998714).

Our reply:

We made the necessary changes.

7. Regarding the Tables: According to the Journal's guidelines, the authors provide an explanatory legend for each table within the text.

Our reply: We already did this before.

8. I think the ‘Conclusions’ paragraph would benefit from some thoughtful as well as in-depth considerations by the authors, because as it stands, it lists down all the main findings of the research, without really stressing the theoretical significance of the study. Authors should make an effort, trying to explain the theoretical implication as well as the translational application of their research.

Our reply: conclusion was updated.

9. In according to the previous comment, I would ask the authors to better define a ‘Limitations and future directions’ section before the end of the manuscript, in which authors can describe in detail and report all the technical issues brought to the surface.

Our reply: we made the requested changes.

10. Regarding the Figures and the Tables: Please provide an explanatory caption for each figure and table within the text.

Our reply: we already made this recommendation in the manuscript.

11. According to the Journal’s guidelines, authors should have included the following sections under the “Declarations” heading: ‘Availability of data and material’, ‘Competing interests’, ‘Funding’, ‘Authors' contributions,’ ‘Acknowledgements’, ‘Authors' information.’ Authors should also provide information about ‘Competing interests’, ‘Funding’, ‘Ethics approval and consent to participate’, and ‘Consent for publication’, as this study involves human data.

Our reply: All these suggestions are managed during resubmission according to the journal guidelines. There is no need for Ethics approval and consent to participate, and ‘Consent for publication’, as this study did not involve human data as it is a review article and not research.

Overall, the manuscript contains three figures, two tables, and 128 references. I hope that, after these careful revisions, this paper can meet the Journal’s high standards for publication. I am available for a new round of revision of this paper. I declare no conflict of interest regarding this manuscript. Best regards, Reviewer

Our reply: Thank you very much.

Reviewer 2:

Thank you for the manuscript with an interesting topic. Please, add some more additional subjects to discuss for the reader.

It is an important topic, and I suggest accepting it with minor consideration.

Our reply: Thank you very much.

Minor consideration

line 71-71 Repetition should be avoided.

Our reply: correction was done.

line 644-645 Repetition of vitamin D

Our reply: correction was done.

Major consideration

Please specify the pathophysiology of ASD development in more detail in each virus infection.

Our reply: we made the needed changes.

An additional schematic picture of the general/common pathophysiology of the relationship between viral infection and ASD may help the reader to understand the process (including the involvement of inflammation with the cytokines storm or etc). Add the cellular or molecular process.

Our reply: The figure was added (figure 2)