



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
<https://www.wjgnet.com>

PEER-REVIEW REPORT

Name of journal: *World Journal of Virology*

Manuscript NO: 83899

Title: Viruses and Autism: A Bi-mutual cause and effect

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05356714

Position: Editorial Board

Academic degree: PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Indonesia

Author's Country/Territory: Bahrain

Manuscript submission date: 2023-02-15

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-02-15 23:47

Reviewer performed review: 2023-02-16 00:30

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



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Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Thank you of the manuscript with interesting topic. please, add some more additional subject to discuss for the reader

PEER-REVIEW REPORT

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Manuscript NO: 83899

Title: Viruses and Autism: A Bi-mutual cause and effect

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05688164

Position: Peer Reviewer

Academic degree: BSc, MD, PhD

Professional title: Research Fellow

Reviewer's Country/Territory: Hungary

Author's Country/Territory: Bahrain

Manuscript submission date: 2023-02-15

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-02-22 09:04

Reviewer performed review: 2023-02-27 08:48

Review time: 4 Days and 23 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

27 February 2023 Review report on the manuscript titled 'Viruses and Autism: A Bi-mutual cause and effect' by Al-Beltagi M et al., submitted to World Journal of Virology Manuscript ID: 83899 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 the viral infection during the critical period of development 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 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. 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 current issue addressed to this special issue (one sentence). The short summary closes with one to two sentences which 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. Please expand 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 on 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. 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 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. 4. The objectives of this study are generally clear and to the point; however, I believe that there are some ambiguous points that 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 state 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. 5. Specific Viral Infections and the Risk of Developing Autism: I was wondering, why did not the authors 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? 6. Discussion: In this final section, authors described the results and their argumentation and captured the 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 mechanism of inflammatory transformation of specific cell type 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>). 7. Regarding the Tables: According to the Journal's guidelines, Authors provide an explanatory legend for each table within the text. 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. 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. 10. Regarding the Figures and the Tables: Please provide an explanatory caption for each figure and table within the text. 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 involve the use of human data. 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

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Virology*

Manuscript NO: 83899

Title: Viruses and Autism: A Bi-mutual cause and effect

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05688164

Position: Peer Reviewer

Academic degree: BSc, MD, PhD

Professional title: Research Fellow

Reviewer's Country/Territory: Hungary

Author's Country/Territory: Bahrain

Manuscript submission date: 2023-02-15

Reviewer chosen by: Yu-Jie Ma

Reviewer accepted review: 2023-04-07 08:01

Reviewer performed review: 2023-04-07 16:18

Review time: 8 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

7 April 2023 The 2nd Review report on the manuscript titled 'Viruses and Autism: A Bi-mutual cause and effect' by Al-Beltagi M et al., submitted to World Journal of Virology Manuscript ID: 83899 Dear Authors, I am pleased to see that the authors took my comments seriously and have solved the issues I raised in the previous round of peer-review session. Currently, the manuscript is a well-written and nicely presented research article presenting the current status of knowledge on the possible effects of the viral infection during the critical period of development on the risk of developing autism. I believe that the manuscript meets the journal's high standard for publication. I am looking forward to seeing more papers written by the same authors. Thank you. I declare no conflict of interest regarding this manuscript. Best regards, Reviewer