

Reply to authors

Reviewer #1:

The title of the manuscript is very attractive, and the content of the paper should also be meaningful if the author modifies the content. There are some concerns.

1. The full text should be written around the effect of a fever in viral infections, but several chapters in this paper deviate from this theme. For example, in the fifth part of the article "effect of extreme hyperthermia on the host ", the content is rarely related to viruses, and in part 5.1, it is even more about "injury", which completely deviates from the theme.

Authors' Reply (AR): We have added a discussion in the opening paragraph of this section to explain that while much of the data on the damage from hyperthermia come from non-infective causes, it is likely that the cause of the hyperthermia is less relevant, and it is the presence of the fever, rather than the cause, that is important. We therefore believe that the data from non-infective causes also applies to a fever in infective causes. Section 5.1 in the original version of this paragraph mentions the viral fever pathway, and IL-6 levels in influenza viral infection. We have added 'The mechanism of injury in hyperthermia, whether due to an infective or non-infective cause...' at the beginning of the paragraph, which we hope will further relate the paragraph to viral infections.

2. Some content in the article should be written in the relevant paragraphs. For example, the last two paragraphs "Viruses, from the Latin word virus, meaning poison, are tiny ubiquitous microorganisms, usually a few hundred nanometers in size. A virion contains a single nucleic acid (RNA or DNA) core surrounded by a protein coat, and requires the cellular processes of animals, plants, and bacteria in order to replicate." and "Coronaviruses are a group of related single-stranded, positive-strand large RNA viruses that cause diseases in mammals and birds. In humans, these viruses cause respiratory tract infections that can range from mild (for example, the common cold), to lethal (for example, SARS, MERS, and SARS-CoV-2). They have characteristic club-shaped spikes that project from their surface, similar to the solar corona, from which their name derives." in the introduction should be written in the third part "effect of fever on virus".

AR: we have moved these paragraphs to the start of section 3, as advised.

3. The author can also list several viral diseases that can cause fever and write down the influence of different degrees of fever.

AR: We have added a table to classify viruses, and offered examples of viral diseases that can cause fever. We could not find evidence to highlight different fevers between each category, which depends on the virulence and on the host response. We have added this

statement to the paper. We hope the effect of different degrees of fever has been covered in the remainder of the paper.

Reviewer #2:

Major comments:

1. In this paper, mild fever, extreme hyperthermia, higher degrees of fever (around 39-40°C) were employed. Could authors define the scope of these different fevers? e.g. what range of temperatures refers to mild fever? And what range of temperatures refers to extreme hyperthermia? It is noted in "4. EFFECT OF MILD FEVER ON THE HOST", "temperatures between 35 and 41.5°C" was described in "4.4. Effect on pharmacology", could "temperatures between 35 and 41.5°C" be defined as mild fever?

AR: We thank the reviewer for their comments. We have added to the introduction a brief description of different degrees of fever, and a comment about the lack of consensus. In the remainder of the article, specific temperatures are mentioned, rather than a description. We have changed the titles of the 4th and 5th sections, to discuss the beneficial and detrimental effects on the host, respectively, rather than 'mild' and 'extreme' which we hope will add clarity. The 'Effect on Pharmacology' section is now entitled 'Effect of Fever on Host Immunity'.

2. In "3.1. Basic viral replication", "This requires interaction with a specific receptor on the host cell surface, allowing fusion of the host cell and viral membranes, or endocytosis.", there are alternative mechanisms for some viruses to enter the host cells, e.g. non-receptor mediated entry by macropinocytosis might be employed by African swine fever virus (ASFV), and ASFV infection in pigs often result in high fever in hosts (Front. Vet. Sci. 7:215. doi: 10.3389/fvets.2020.00215). Authors might add this information in this paper.

AR: we are grateful to the reviewer for this additional information, and have added it to the paper.

Minor comments:

1. "High temperatures appear to increase endosomal pH, adversely affecting influenza entry and intracellular transportation" should be "High temperatures appear to increase endosomal pH, adversely affecting influenza virus entry and intracellular transportation"

AR: agreed – manuscript changed.

2. "A raised temperature also appears to cause a reduction in the cytokine IL-6 levels after human cell infection with influenza" should be "A raised temperature also appears to cause a reduction in the cytokine IL-6 levels after human cell infection with influenza virus".

AR: agreed – manuscript changed.

Reviewer #3:

This paper has briefly reviewed the effect of fever in acute infections, and suggested that a mild fever promoted host defence mechanisms and reduced viral replication. whereas, a high fever is detrimental. however, Manuscript, based on literature review, was lack of innovative and creative.

AR: Thank you to the reviewer for their comments. The manuscript was an invited review, with the content and format discussed and agreed with the editorial office before submission, and we are grateful that the reviewer recommended accepting the paper in its current format. We have therefore not edited the manuscript in an attempt to make it more innovative and creative, but will do so if required by the editorial office. We would be grateful for further guidance on how to make the paper more creative, if this is required.

5 EDITORIAL OFFICE'S COMMENTS

(1) I found no “Author contribution” section. Please provide the author contributions.

AR: now added

(2) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

AR: now uploaded as a powerpoint file.