

We would like to thank the editors and reviewers for their support and helpful suggestions regarding our paper entitled “Phage therapy: An alternative to antibiotics in the age of multi-drug resistance.” We have responded to each point. We believe that the revised manuscript is now stronger because of the changes recommended by the reviewers. We have referenced the reviewers’ comments and described the corresponding changes below.

Thank you for your time,
Derek M. Lin

Reviewer 00504975	
Reviewer Comments	Changes
Page 4. “... 262.5 million treatment courses prescribed in 2011 alone (842 prescriptions per 1000 persons) and 25,000 tons of antibiotics used between medicine and agriculture each year” Are these numbers for the USA? Please clarify.	Agreed, revised to: “262.5 million treatment courses prescribed in the US in 2011 alone (842 prescriptions per 1000 persons) and an estimated 100,000-200,000 tons of antibiotics used globally between medicine, agriculture, and horticulture each year.”
Page 5. “... regulatory organizations such as the CDC and WHO have declared antibiotic resistance a global crisis.” Consider citing a reference to support this statement.	Citations added
Page 5: “In the years of 1983-1987, there were 16 new pharmaceutical antibiotics approved by the FDA for use in the US, this number has steadily trended downwards and between 2003-2007 only 5 new antibiotics were approved” Can you please provide more current information, let’s say for the last 9-10 years (i.e., 2006-2016)?	Revisions made to include more recent data: “this number has steadily trended downwards and between 2010-2016 only 6 new antibiotics were approved ^[10] .”
Page 6: “the greatest and most urgent global risk.” Please provide a reference to support this statement.	Citation provided.
Page 6: ... “which are the most numerous members of Earth’s biosphere.” Please delete, it was already mentioned at the beginning of	Deleted

the introduction.	
Page 10: In the first line it reads "hampster" instead of "hamster". Please amend.	Fixed
Page 12: Consider citing a reference to support the statement in the first half of the first paragraph: "Two major protein classes... allowing the lysin proteins to access and hydrolyze the cell wall."	Citation added
Page 12: <i>A. baumannii</i> is mentioned for the first time, please indicate the genus in full for this microorganism.	Fixed
Page 13: The percentage numbers in "...cleared infections in 92% of mice, whereas a combination of 3 previously identified lysines achieved only an 80% survival rate" are irrelevant without knowing the total number of animals or if the differences (92% vs. 80%) were significant.	A single dose administered intraperitoneally to mice in a mixed <i>S. pyogenes</i> and MRSA bacteremia model provided a significantly higher survival rate than treatment with 3 previously characterized lysins ^[64] .
Page 13: "S. Aureus" should be <i>S. aureus</i> "; it happened twice.	Fixed
Page 14: Cited references at the end of the first paragraph reads "[70-62]", should it be "[70-72]"? Please amend.	Fixed
It seems that the section "PHAGE THERAPY VERSUS ANTIBIOTIC THERAPY" would have been written by a different person. Consider reediting some of the paragraphs.	The input from the reviewer is appreciated but I'm unsure of the exact meaning. Would the reviewer be able to clarify? As of now this section has been left as is.
Page 15: Please review grammar for "an host" and "an healthy".	Fixed. Corrected to "a host" and "a healthy"
Page 15: Please delete "The researchers" from "The researchers Tetz and Tetz..."	Deleted
Page 17: Please delete "at the Eliava Institute of Bacteriophages in Tbilisi, Georgia".	Deleted
Abbreviations Although some abbreviations are commonly used worldwide and do not require to be described in full (e.g. WHO, HIV/AIDS, UK, EU, US/USA), others	<ul style="list-style-type: none"> • "CDC," "FDA," and "MRSA" all given full name before acronym. • "UN" and "ETEC" acronyms removed, full name used instead.

<p>may do require to be described in full when first used in the manuscript. For instance CDC, FDA, MRSA, UN, ETEC. Also, "CRISPR/Cas" was first used in page 7, but described in full in page 11, and "ARGs" was described in full in page 4 and again in page 18. Please amend. Abbreviations should be consistent throughout the manuscript. For instance, US (in pages 4 and 5) and USA (in page 11) are both used; please amend. Abbreviations should only be used when the term is used more than once throughout the manuscript. "(CIC)" is used in page 15, but nowhere else; please delete it.</p>	<ul style="list-style-type: none"> • "CRISPR/Cas" explained in full at first reference on page 7 instead of on page 11 • "ARG" as an acronym replaced with "antibiotic resistance genes." • "USA" changed to "US" for consistency. • "CIC" removed.
<p>References Please check references so that they comply with WJGPT guidelines. For dates, only the year, but not the month, is necessary. The volume, but not the number, of the journal is necessary. Use italics for the names of microorganism and other Latin terms (e.g., in vitro, in vivo) (e.g., references 22, 54). Use sentence case for the title (e.g. references 13, 35, 48, 53, 56).</p>	<p>All references changed to fit the format outlined by WJGPT guidelines.</p>
<p>Please provide the complete reference for reference no. 52</p>	<p>Complete reference added</p>

Reviewer 00012309	
Reviewer Comments	Changes
<p>Current literature contains a few hints at the use of phages as "biocontrol tools", namely to try and lower the entering of bacteria into the food chain. Would the Authors consider it worth to spend a few words on this issue?</p>	<p>Addition of detail on phages as biocontrol on page 11:</p> <p>"However, in the food industry, there are several commercial phage preparations used for biocontrol of bacterial pathogens that are approved by the FDA under the classification of "generally considered as safe." These</p>

	<p>preparations are used against <i>Salmonella</i> spp., <i>Listeria monocytogenes</i>, MRSA, <i>E. coli</i> O157:H7, <i>Mycobacterium tuberculosis</i>, <i>Campylobacter</i> spp., and <i>Pseudomonas syringae</i> among others[53-54]. Phages also have potential value for pathogen detection such as using bioluminescent reporter phage to detect <i>Bacillus anthracis</i>[56]. In 2011 there was an estimated 48 million cases of food poisoning in the United States alone[55]. Evidence suggests that phage biocontrol can be an effective method for improving food safety at numerous stages in meat production and processing, and also has potential to reduce bacterial contamination in fruits, vegetables, and dairy products[55]. These investigations into phage biocontrol in food production, as well as recent placebo-controlled human trials that demonstrated the safety of oral phage administration[57-60], are gradually beginning to fill the knowledge gap in phage therapy safety."</p>
--	---

Reviewer 00504911	
Reviewer Comments	Changes
<p>"However, the complexity of the matter and the long list of exemplifications reported tend to reduce the attention of the reader. It is strongly suggested (recommended) to add some tables, in order to summarize the exemplifications reported and described, and some figures to represent the different mechanisms and activities described. These iconographies would improve significantly the review and cannot be avoided."</p>	<p>Two tables added summarizing the exemplifications reported in the manuscript.</p>