

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Probiotics administered intravaginally as a complementary therapy combined with antibiotics for the treatment of bacterial vaginosis: a systematic review protocol
<b>AUTHORS</b>	Ma, Liyan; Su, Jianrong; Su, Yanli; Sun, Wei; Zeng, Zhaoying

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Piotr Heczko Chair of Microbiology, Jagiellonian University Medical College, Krakow, Poland.
<b>REVIEW RETURNED</b>	02-Jan-2017

<b>GENERAL COMMENTS</b>	<p>Intro, line 17: term "H2O2 producing lactobacilli" seems to be outdated. Complex and high population of the lactobacilli in vaginal microbiota are regarded as protective against BV. Moreover, hydrogen peroxide is not produced in anaerobic conditions in vivo.</p> <p>Intro, line 23: both killing and growth inhibiting activity of antibiotics is important in suppressing anaerobes in vagina.</p> <p>Methods, lines 8-9: analysis of the trials based on Amsel's criteria should be done separately from those based on Nugent score. Application of Nugent score in diagnosing BV separates so-called "intermediate" flora or "aerobic vaginitis" in European terminology. Overgrowth of aerobic bacteria in vaginal microbiota cannot be treated with standard antibiotics used in BV.</p>
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<b>REVIEWER</b>	Dr Santosh S Waigankar Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai INDIA
<b>REVIEW RETURNED</b>	20-Mar-2017

The reviewer completed the checklist but made no further comments.

<b>REVIEWER</b>	David G. Bostwick MD Bostwick Laboratories United States of America
<b>REVIEW RETURNED</b>	10-May-2017

<b>GENERAL COMMENTS</b>	This report presents the protocol for a systematic literature review of the role of probiotics in treating bacterial vaginosis. The protocol is sufficiently detailed and scientifically rigorous that it could serve as a template for other structured reviews.
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<b>REVIEWER</b>	Diane Chapman Utah HealthCare Institute
<b>REVIEW RETURNED</b>	21-May-2017

<b>GENERAL COMMENTS</b>	<p>1) There are many misspellings and grammatical errors in the text - please edit document for English grammar</p> <p>2) I would like to see more discussion about how this study protocol addresses all of the PRISMA-P checklist.</p> <p>3) Please address any additional limitations of the study - e.g. will there be any limitations in sample size?</p> <p>4) Many of the reference articles were published &gt; 10 years ago. I would prefer to see the inclusion of more recent reference articles.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Piotr Heczko

Institution and Country: Chair of Microbiology, Jagiellonian University Medical College, Krakow, Poland.

Please state any competing interests: None declared

Please leave your comments for the authors below

Intro, line 17: term "H<sub>2</sub>O<sub>2</sub> producing lactobacilli" seems to be outdated. Complex and high population of the lactobacilli in vaginal microbiota are regarded as protective against BV. Moreover, hydrogen peroxide is not produced in anaerobic conditions in vivo.

Intro, line 23: both killing and growth inhibiting activity of antibiotics is important in suppressing anaerobes in vagina.

Response: I agree with the reviewer completely. Physiological concentrations of H<sub>2</sub>O<sub>2</sub> produced no detectable inactivation of BV-associated bacteria in vitro. Moreover, H<sub>2</sub>O<sub>2</sub> can not be produced in anaerobic conditions vivo. It has been revised as below.

Intro, lines 7-10: Previous studies have shown that a complex and high population of the lactobacilli in vaginal microbiota are regarded as protective against BV, which is typified by a profound overgrowth of vaginal anaerobic bacteria.

Intro, lines 12-13: Both the killing and growth inhibiting activities of antibiotics are important towards suppressing anaerobes in the vagina.

Methods, lines 8-9: analysis of the trials based on Amsel's criteria should be done separately from those based on Nugent score. Application of Nugent score in diagnosing BV separates so-called "intermediate" flora or "aerobic vaginitis" in European terminology. Overgrowth of aerobic bacteria in vaginal microbiota cannot be treated with standard antibiotics used in BV.

Response: Thank the reviewer for the great help. We think it is very important to separate aerobic vaginitis from BV of the Nugent score 7-10. It has been revised as below.

Methods, lines 18-19: Analyses of the trials based on Amsel's criteria will be performed separately from those based on the Nugent score.

Reviewer: 2

Reviewer Name: Dr Santosh S Waigankar

Institution and Country: Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai INDIA

Please state any competing interests: None declared

Please leave your comments for the authors below  
None

Reviewer: 3

Reviewer Name: David G. Bostwick MD

Institution and Country: Bostwick Laboratories, United States of America

Please state any competing interests: None declared

Please leave your comments for the authors below

This report presents the protocol for a systematic literature review of the role of probiotics in treating bacterial vaginosis. The protocol is sufficiently detailed and scientifically rigorous that it could serve as a template for other structured reviews.

Response: Thank you for your encouragement.

Reviewer: 4

Reviewer Name: Diane Chapman

Institution and Country: Utah HealthCare Institute

Please state any competing interests: None declared

Please leave your comments for the authors below

1) There are many misspellings and grammatical errors in the text - please edit document for English grammar

Response: It was done. We asked American Journal Experts to help us edit our manuscript.

2) I would like to see more discussion about how this study protocol addresses all of the PRISMA-P checklist.

Response: Our manuscript is just a protocol and we will discuss much more in our full review and meta-analysis.

3) Please address any additional limitations of the study - e.g. will there be any limitations in sample size?

Response: It was done as below.

Strengths and limitations of this study, lines 10-14: Our review and meta-analysis intends to combine the results of different studies that have comparable effect sizes to be computed. However, it may be that we will only obtain a small sample size and limited number of studies, which might influence the validity and reliability of the conclusions.

4) Many of the reference articles were published > 10 years ago. I would prefer to see the inclusion of more recent reference articles.

Response: Thank you for your well-intentioned suggestion. It was done. We have updated 11 reference articles which were published < 5 years. Details see the references list in the manuscript.

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Piotr Heczko Chair of Microbiology, Jagiellonian University Medical College, Krakow, Poland
<b>REVIEW RETURNED</b>	19-Jul-2017

The reviewer completed the checklist but made no further comments.