Reviewing Manuscripts for Journals

Michael D. Cabana, MD, MPH

December 29, 2023

How many of you have reviewed a manuscript for a journal?

How was the experience?

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Objectives

- To discuss the components of a manuscript review
- To review tips for providing useful manuscript reviews

Reviewing Manuscripts

- Reviewing manuscripts is an important part of the peer review process
- Manuscript reviewers (or peer reviewers) are critical for the process to work well

Peer reviewers can help editors assess which of the following manuscript characteristics?

A. Validity of the conclusions (external validity)
B. Validity of the methods (internal validity)
C. Ethical issues in the design and conduct of the study
D. Originality of the study
E. All of the above

Peer reviewers can help editors assess which of the following manuscript characteristics?

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D. Originality of the study
E. All of the above

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What is Peer Review?

- A process to assess the validity, quality and originality of a potential article for publication
- Provides another assessment of potential ethical or compliance issues.
- The process should improve the quality of the manuscript when it is eventually published

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Peer review is the central pillar of trust for researchers

84%

of researchers believe that without peer review there would be no control in scientific communication.

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Why Serve as a Manuscript Reviewer?

A. It pays well ($200/review)
B. It is required for promotion to Associate Professor (50 reviews) and Full Professor (150 reviews)
C. It will help you improve your own writing
D. You have to review a manuscript if you are asked by an editor to review a manuscript
E. All of the above

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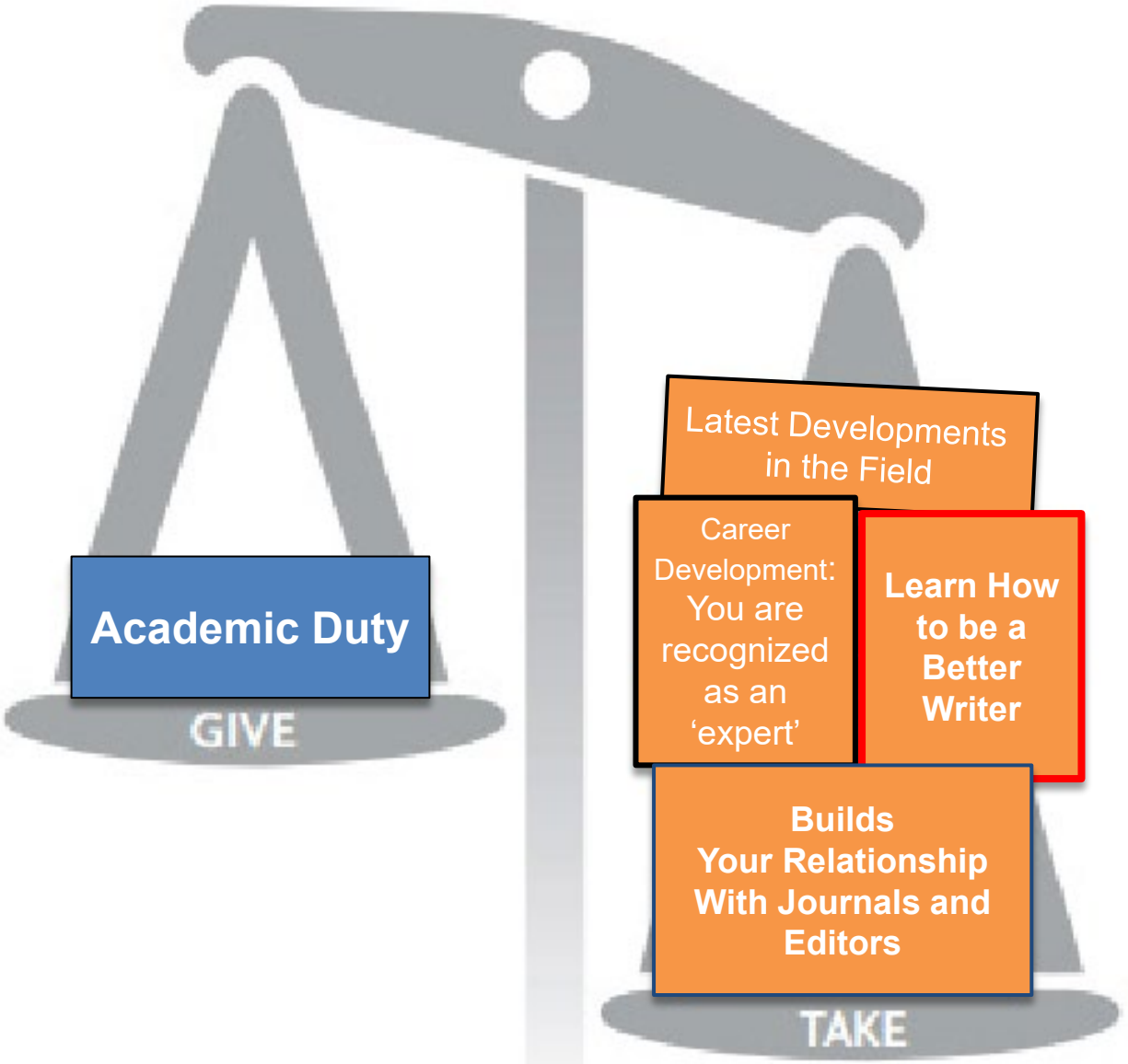

Based on https://www.elsevier.com/connect/how-to-review-manuscripts-your-ultimate-checklist

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pediatricseditorial@aap.org | Michael Cabana | 1 | Thu 9,

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MS TITLE: [redacted]

MS AUTHORS: [redacted]

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I am writing to invite you to review this Review Article for Pediatrics.

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If this article type has an abstract, it is included at the end of this email and in your Reviewer Area. (Several article types have no abstract.)

Pediatrics offers 3 continuing medical education credits for manuscript peer review, provided the review meets timeliness and quality/relevancy qualifications contained in the reviewer guidelines. For more information and to ensure successful participation in this CME activity, please see the attached document. This activity also is eligible for MOC Part 2 points. To earn MOC points, reviewers must score a 3 on a 3-point scale. (A 3 indicates the review was submitted on time and was highly relevant.) Reviewers who receive a 3 will receive an email with information on how to claim MOC Part 2 points. MOC points will be awarded quarterly. Reviewers who score a 1 or 2 will not receive MOC Part 2 points or CME credit and will not receive a follow-up communication.

*Should we receive a sufficient number of reviews before your three-week deadline, the editors may choose to make a decision on the manuscript. You will be notified by e-mail if a decision is made. At that time, the manuscript and score sheet will be removed from your reviewer area. If you still wish to submit comments, e-mail them to the editorial office and they will be forwarded anonymously to the authors.

P

pediatricseditorial@aap.org | Michael Cabana

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MS AUTHORS: [redacted]

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If you receive an e-mail from an editor, who requests you to complete a review, do you have to review the manuscript?

A. Yes

B. No

If you receive an e-mail from an editor, who requests you to complete a review, do you have to review the manuscript?

A. Yes

B. No

How many manuscript reviews is a faculty member expected to complete each year?

How many manuscript reviews is a faculty member expected to complete each year?

It depends. Many people will give you many different answers

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Kerry-Ann Mitchell MD PhD
@DrKerryMitchell

For folks peer **reviewing**, **how many manuscripts** on average are you **reviewing** in a month? What's a reasonable number? I get so **many** to review and feel bad when I have to decline! @OpenAcademics #medtwitter #AcademicChatter #AcademicTwitter

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1 Retweet 14 Likes

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Tracey Perez Ko... · 3/26/20
Replying to @DrKerryMitchell and @OpenAcademics

If I do 3-4 a year, it is a lot. Also, if a journal for which I review does not send my submission out for peer review, I no longer review for that journal.

4 4

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Roxana Daneshjo... · 3/26/20
Replying to @DrKerryMitchell and @OpenAcademics

I don't think I could do more than one a month, honestly.

1 5

For every manuscript that you submit, an editor has to find 3 reviewers

As a rule of thumb:

$$\frac{\text{\# of submissions}}{\text{Year}} \times \frac{\text{3 reviews}}{\text{submission}} = \frac{\text{\_\_ reviews}}{\text{Year}}$$

Starting the Manuscript Review

- Clear your mind
  - Your job is to be helpful to the editor and to the authors
  - It is okay to be skeptical, but don't be cynical
- Read the entire manuscript (including all the tables and appendices)
- Develop a general impression & summary
- List your major concerns
- List your minor concerns

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A Randomized Controlled Trial of Early Probiotic Supplementation for Eczema and Asthma Prevention

Michael D. Cabana, MD, MPH (1,2,4), Michelle McKean, RD, MPH (1),
Aaron B. Caughey, MD, PhD (7), Lawrence Fong, MD (3)
Susan Lynch, PhD (3), Angela Wong, MD (5), Russell Leong, MD (6)
*Homer A. Boushey, MD (3) and *Joan F. Hilton, ScD, MPH (2)

From the (1) Department of Pediatrics, (2) Epidemiology and Biostatistics (3) Medicine and (4) the Philip R. Lee Institute for Health Policy Studies, University of California, San Francisco (UCSF) and (5) the Department of Pediatrics, Kaiser Permanente, San Francisco. (6) Department of Pediatrics, California Pacific Medical Center, San Francisco, CA and (7) the Department of Obstetrics and Gynecology, University of Oregon Health Sciences, Portland, OR.

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Fax:	415-476-6106
Word Count:	(abstract: 338)
Conflicts of Interest	None of the authors report conflicts of interest.

* Drs. Homer Boushey and Joan Hilton contributed equally as senior authors for this study.

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September 5, 2016

Lewis First, MD
Editor-in-Chief, *Pediatrics*
University of Vermont College of Medicine
Chief of Pediatrics
Vermont Children's Hospital at Fletcher Allen Health Care
Given Courtyard S-250
Burlington, Vermont 05405

Dear Dr. First,

Enclosed, please find an electronic copy of the manuscript, "A Randomized Controlled Trial of Early Probiotic Supplementation for Eczema and Asthma Prevention" for submission to *Pediatrics*.

Recent studies of early probiotic supplementation in infancy have investigated the potential benefit in decreasing the risk of allergic disease and early markers of asthma, such as eczema. Based on the hygiene hypothesis, which suggests that the absence of infectious exposure at a critical point in immune system development could lead to greater risk of allergic disease, it is thought that probiotic exposure could theoretically affect immune system development and reduce the subsequent risk for development of allergic disease

We report the results of the Trial of Infant Probiotic Supplementation (TIPS) Study, a double-blind, randomized controlled trial (RCT) of the effectiveness of early infant *Lactobacillus rhamnosus* GG (LGG) supplementation on the later development of childhood eczema and asthma. We recruited 184 infants over six years and we now report the results, as the youngest child has now reached 2 years of age.

At 2 years, the estimated cumulative incidence of eczema was 30.9% (95% confidence interval [CI], 22.5- 41.5%) for the control arm and 28.7% (95% CI, 20.5- 39.2%) on the LGG arm (p=0.55). At the 6 year mark, the cumulative incidence of asthma was 27.3% (95% CI, 17.7-40.6%) on the control arm and 25.5% (95% CI, 16.8 - 37.5%) on the LGG arm (p=0.25). In exploratory analysis of 48 infants born via cesarean, the cumulative incidence of asthma was 0.31 (95% CI, 0.16 – 0.46) in the control arm and 0.22 (95% CI, 0.11-0.34) in the LGG arm at 5.5 years of age (p=0.06).

-----Original Message-----
From: onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com
[mailto:onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com]
Sent: Monday, October 10, 2016 6:32 AM
To: Cabana, Michael <Michael.Cabana@ucsf.edu>
Subject: PEDIATRICS: Decision Letter - MS# 2016-3000

10-Oct-2016

RE: Manuscript 2016-3000

A Randomized Controlled Trial of Early Probiotic Supplementation for Eczema and Asthma Prevention

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Dear Dr. Cabana:

The editors of Pediatrics feel that your manuscript has merit but would require substantial work before it could be reconsidered for publication. You are welcome to submit a revised manuscript, which will be sent out for peer review; referees may include past and new reviewers. Please be aware that fewer than half of such papers are ultimately accepted.

If you decide to resubmit this manuscript, you must address the reviewer concerns included at the end of this e-mail. Your successful response to the critiques of the current reviewer(s) does not guarantee acceptance of the manuscript, because new reviewers may be added for the revised paper and may have different concerns.

In addition to the reviewer comments below, please address the following item from the editors:

* Add a Table of Contents Summary to your title page, placed before the “What’s Known/What’s Added” summaries. For published articles, the Table of Contents Summary will appear under the author names in the table of contents to give the reader a brief insight into what the article is about. It should entice

Specific Comments are Numbered

Reviewer: 2

Comments to the Author:
This is a well-designed and conducted randomized clinical trial on the protective effects of probiotics on eczema in children. This is a clinically relevant issue, with direct impacts on clinical care and public health. The results were unfortunately non-significant, but that does not make the findings less important. Many parents and doctors are faced with the question whether probiotics are useful, particularly given its availability for the general public. I do have some questions regarding the analysis.

Short summary

1. The authors mention studies by Kopp et al. and Kalliomaki et al. to have conflicting results and suggest this could be based on underlying environmental exposures. In the introduction I advise to also describe how the authors aimed to solve this particular problem in their study. Secondly, in order to value the impact of the two previous studies I suggest to mention the sample sizes of both previous studies in the introduction.

2. Was this RCT registered in the ClinicalTrials register and were primary outcomes and any predefined subgroup analyses noted before start of the study? If so, please mention in article, with reference number.

3. My main question is with respect to the outcome. The authors chose a time-to-event analysis. Although I agree it is important to know if probiotics can delays or reduces the onset of eczema, it remains an important question whether the prevalence of "active" eczema in early childhood. Much like asthma in early childhood eczema is a fluctuating disease that in some children resolves completely before school age. Did the authors investigate the outcome of active eczema at the given ages of 2, 3, 4, 5 or 6 years? I understand this will decrease sample sizes, but I do think it is an important question to investigate as a secondary analysis.

Major Concerns

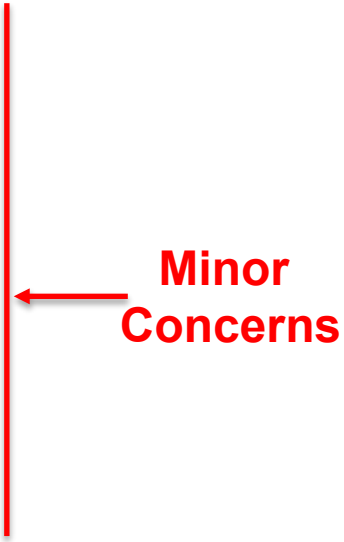
a. Table 1: I think birth length and head circumference can be eliminated. The pregnancy and postnatal feeding and breastfeeding rows are empty as they connote subtopics; however, the horizontal lines in the table make it look like they are empty rows. Format the table to clarify the subsections. Do the same for Table 2.

b. Figure 2; no issues. However, the caption notes the calculation was at age 2.5 years and the text says the primary outcome was incidence within 2 years of age. I would use the same terminology (precise age) in the text and figure.

c. Figure 3. Cumulative incidence of asthma is depicted up to age 5 years, but the text reports the cumulative incidence at age 6 years. The figure and text should be consistent. Only 30-40 subjects comprised each group at 5 years, and the lower numbers increase the risk of false negative results.

d. I would delete figure 4. There are too few participants to draw any firm conclusions, and this result can be adequately addressed in the text alone.

e. The check lists and consort diagram template can be deleted from the final manuscript.



Next steps

- Your comments are sent back to the author(s)
- The manuscript is revised based on your comments
- The author(s) respond point-by-point to each comment and show how they incorporated the comment (or did not incorporate the comment)

-----Original Message-----
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To: Cabana, Michael; McKean, Michelle; caughey@ohsu.edu; Fong, Lawrence; Lynch, Susan; Wong, Angela; airleong@hotmail.com; Boushey, Homer A; Hoppe, Patricia; Hilton, Joan
Subject: Thank you for your manuscript submission to Pediatrics

05-Apr-2017

Manuscript ID: 2016-3000.R1
A Randomized Controlled Trial of Early Probiotic Supplementation for Eczema and Asthma Prevention

Dear Dr. Michael Cabana and Colleagues:

Thank you for submitting your article(s) to Pediatrics. This is an automated reply that has been sent to all authors on the manuscript so that everyone designated as an author is aware of the submission. If you feel that you do not meet author criteria, or were unaware that you were listed as an author, please contact PediatricsEditorial@aap.org. All future correspondence will be directly with the submitting author.

If you submitted a new MANUSCRIPT, it will be screened and possibly peer-reviewed. The peer-review process may take eight weeks or more. If your manuscript is accepted, it will be published online. The editors determine later if an accepted paper also will appear in the print edition.

If you submitted a REVISED manuscript or supplement, your submission retains its previous ID number but is appended with ".R1" or ".R2" depending on the version.

If you submitted a SUPPLEMENT (single article or multiple articles), it will be peer-reviewed. The submitting author will be notified of a decision within approximately two months.

The submitting author can review the status of the submission online by logging in at https://mc.manuscriptcentral.com/pediatrics and checking their author center.

We will contact the submitting author as soon as possible with our decision.

Sincerely,

Lewis R. First, MD
Editor-in-Chief
Pediatrics Editorial Office
University of Vermont College of Medicine
89 Beaumont Ave, Given D201
Burlington, VT 05405-0068

A Randomized Controlled Trial of Early Probiotic Supplementation for Eczema and Asthma Prevention

Michael D. Cabana, MD, MPH (1,2,4), Michelle McKean, RD, MPH (1), Aaron B. Caughey, MD, PhD (7), Lawrence Fong, MD (3); Susan Lynch, PhD (3), Angela Wong, MD (5), Russell Leong, MD (6) Homer A. Boushey, MD (3) and Joan F. Hilton, ScD, MPH (2)

Affiliations: (1) Department of Pediatrics, (2) Epidemiology and Biostatistics (3) Medicine and (4) the Philip R. Lee Institute for Health Policy Studies, University of California, San Francisco (UCSF) and (5) the Department of Pediatrics, Kaiser Permanente, San Francisco. (6) Department of Pediatrics, California Pacific Medical Center, San Francisco, CA and (7) the Department of Obstetrics and Gynecology, University of Oregon Health Sciences, Portland, OR.

Address correspondence to: Michael D. Cabana, MD, MPH, 3333 California Street, Laurel Heights Bldg #245, San Francisco, CA 94118 [michael.cabana@ucsf.edu] 415-514-2660

Short Title: Early Probiotics for Eczema and Asthma Prevention

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Funding Source: Funded by the National Institutes of Health (HL 080074) and the Clinical and Translational Science Institute (UL1 RR024131) at UCSF.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Clinical Trial Registration: ClinicalTrials.gov identifier: NCT00113659

Abbreviations: CA indicates California; CFU, Colony forming units; CI, Confidence interval; CT, Connecticut; HR, Hazard ratio; LGG, *Lactobacillus rhamnosus* GG; SD, Standard deviation; TIPS, Trial of Infant Probiotic Supplementation; Th-1, T-helper cell 1; Th-2, T-helper cell 2; UCSF, University of California, San Francisco

Table of Contents Summary: This randomized controlled trial examines the effect of early *Lactobacillus rhamnosus* GG infant supplementation in decreasing the risk of childhood eczema.

What is Known About This Topic: Based on the hygiene hypothesis, probiotic exposure may affect immune system development and subsequent risk for allergic disease; however, recent trials of probiotic *Lactobacillus rhamnosus* GG supplementation in decreasing the risk of childhood eczema and asthma have yielded mixed results.

What this Study Adds: For high-risk infants, early LGG supplementation does not appear to prevent eczema or asthma development at 2 years of age.

List word counts below (do not paste the text here). Please see the Decision Letter Attachment for allowances as they pertain to your manuscript type.

# of words in Abstract: **250** (250 words allowed)
# of words in Manuscript Body: **3642** (3000 allowed for Regular Articles/Quality Reports; 4000 Reviews/Special Articles; 800 Commentaries; 1200 Perspectives)
# of characters in Main Title: **97** characters (97 characters allowed, including spaces)
# of characters in Short Title: **49** (55 characters allowed, including spaces)
# of words in "Table of Contents Summary": **21** (25 words allowed; this section appears in Regular Articles only)
# of words in "What's Known on this Subject": **40** (40 words allowed; this section appears in Regular Articles only)
# of words in "What this Study Adds": **20** (40 words allowed; this section appears in Regular Articles only)

2016-3000.R1 – A Randomized Controlled Trial of Early Probiotic Supplementation for Eczema and Asthma Prevention-- by Cabana et al.

EDITOR/REVIEWER COMMENTS *Paste each of the editor and reviewer queries here.*	**AUTHOR'S RESPONSE** *Paste your answer to the editor and reviewer queries here. If you alter your manuscript to address this query, you MUST paste the relevant altered text here – verbatim as it appears in the manuscript.*	**REFERENCE PAGE** *State where the change will appear in your new revised manuscript.*	**CHANGE APPROVED? FOR EDITORIAL USE ONLY**
EXAMPLE: Reviewer 1's comment	EXAMPLE: A brief response to this reviewer's comment. The text now states: "insert relevant changed text here"	EXAMPLE 1: Page 7, lines 10-22 EXAMPLE 2: No change	
Ed. *Editor's comment:* Add a Table of Contents Summary to your title page, placed before the "What's Known/What's Added" summaries. For published articles, the Table of Contents Summary will appear under the author names in the table of contents to give the reader a brief insight into what the article is about. It should entice the reader to read the full article. Limit your summary to 25 words or fewer. For example: "Through linkage of state Medicaid and Child Protective Services databases, this study captures similarities and differences in health care expenditures based on a history of child maltreatment."	We have added: "Table of Contents Summary: This randomized controlled trial examines the effect of early *Lactobacillus rhamnosus* GG infant supplementation in decreasing the risk of childhood eczema." to the title page.	Title Page	
A1. General Comments: This is a prospective randomized trial evaluating the effect of early probiotic	Thank you for your comment. We are happy to have reached this milestone.	No change	

What the Reviewer Commented

Author Response

	supplementation in infants on the development of eczema and asthma in early childhood. The authors published details of the study design in 2007 and should commended on bringing the study to fruition 9 years later.			
A2.	Of note the original study design and intent vary slightly from the original design reported in 2007. Originally doctor-diagnosed asthma was not an endpoint.	Please also see our response to A11. When we planned the study, we did not anticipate the extended amount of time required for patient recruitment (6 years versus 2 years). When the study was designed, we assumed that when the last enrolled patient would be 2 years of age and the oldest enrolled patients would be 3 to 4 years of age. For children at three years of age, it is difficult to determine if a child has asthma. As a result, we originally used 'wheezing' as an endpoint, as it is part of an algorithm to determine the likelihood of the later development of asthma (Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med*. 2000;162:1403-1406). In our current situation, with much older children, we believe that doctor-diagnosed asthma is a better outcome to use. Since many of the patients are three years and older, and since wheezing was only an 'intermediate' endpoint to help determine the likelihood of asthma, for the analysis of this older population, we believe that 'asthma' was a more appropriate and clinically meaningful endpoint.	Not applicable (NA)	
A3.	Approximately 180 infants with 1 or both parents claiming asthma received probiotics (*Lactobacillus GG*) or a placebo for 6 months, starting at birth. Infants were followed for a minimum of 2 years (not 3 years as in the original study design) and about a quarter were followed for 6 years. This was possible due to the many years of study enrollment. The authors found no effect of probiotics administration on the cumulative incidence of either eczema or asthma. This is a sound study design and the results are valid. However, one	Please see our response to A7.	Not applicable (NA)	

	concern is the low number of subjects available for analysis at 4 and 6 years from enrollment. The study was not really powered to assess differences in asthma incidence at the later ages, given the lower number of participants available for analysis at those time points.			
A4.	Another concern is the demographics. The majority of infants came from highly educated parents with high incomes, which is not representative of the average population. Nevertheless, the study does contribute useful information concerning the use of probiotics infants to attenuate the development asthma and eczema.	Please see the response to A24. We agree with this point. We mention in the conclusion that, "the infants' mothers were older, more affluent and more educated that the typical population." We also added, "As a result, it is difficult to extrapolate the results of this study to rural communities or low income urban settings," as pointed out by the reviewer.	Page 15 Line 2-4	
A5.	Abstract: The sentence in the Objective is more of a background statement. The objective was actually to determine whether probiotic administration during the first 6 months of life could decrease the development of asthma and eczema in childhood.	We agree with this point. We changed the sentence in the objective to read, "To determine whether probiotic administration during the first 6 months of life can decrease the development of childhood asthma and eczema	Abstract Page 3 Line 3-4	
A6.	Abstract Methods: What were the primary and secondary endpoints? State those clearly.	We agree and have clearly listed the primary and secondary endpoints in the abstract. We changed the following from "We conducted a randomized, double-blind controlled trial of early *Lactobacillus rhamnosus* GG (LGG) supplementation on the development of eczema and asthma in infants at high risk for asthma." to the following: "We conducted a randomized, double-blind controlled trial of early *Lactobacillus rhamnosus* GG (LGG) supplementation on the development of eczema (primary endpoint) and asthma and rhinitis (secondary endpoints) in infants."	Abstract Page 3 Line 5-7	

	or the participant discontinued follow-up without a diagnosis ("censoring time"). Since participants who were accrued earlier have more assessments, we avoided bias by using survival analysis methods that account for variable lengths of follow-up.."		
A8. Introduction: I suggest shortening the second paragraph, leaving out some of the details of these studies. The details can be discussed in the Discussion section.	As suggested by the reviewer, we have shortened the second paragraph and left out details of the Kopp study. The section now reads: "In a randomized, controlled, double-blind study of 159 newborns in Finland, Kalliomaki et al. found that early *Lactobacillus rhamnosus* GG (LGG) exposure (1 x 10^{10} CFUs of LGG per day) as a probiotic supplement of both pregnant women and their newborns led to a lower 2-year incidence of atopic disease, including eczema.[3] In addition, follow-up studies found that such effects were sustained past infancy.[4,5] However, a similar study from Germany published by Kopp et al., ~~found no benefit associated with probiotic supplementation of pregnant women and newborns. Except for a slight variation in the dosing schedule, the probiotic interventions were similar to the study published by Kalliomaki et. al. Pregnant women with a family history of atopic disease were randomized to receive either placebo or 5 x 10^{9} CFUs of LGG given twice a day. Kopp et al.,~~ found no significant difference in the development of atopic dermatitis (OR: 0.96; 95% CI: 0.38, 2.33) by 24 months of age.[6] Although both studies recruited women whose infants would be at high risk for asthma, the study populations differed geographically and by rates of breastfeeding exposure. For example, the average duration of breastfeeding was much longer in the study by Kopp et al (9.2 months versus 6.4 months)."	Page 4 Lines 11-20	
A9. Third paragraph (line 56, P 4). What does "these results" pertain to? If it is the results in the studies mentioned in paragraph 2, then combine the paragraphs.	We agree with the reviewer that this sentence ambiguous. We clarified what 'these results' pertain to. The sentence "These results suggest that the effects of probiotic supplementation may vary based on underlying	Page 4 Lines 20-22	

<table>
<tr><td></td><td>Am J Respir Crit Care Med. 2000;162:1403-1406</td><td></td><td></td></tr>
<tr><td>A12a. Participants were selected at birth if either parent had a history of asthma. How was the asthma history in parents corroborated or determined?</td><td>Parental history of asthma was determined by the parent's own report that they were diagnosed with asthma by a physician. The text states, "Eligible newborns had at least one biologic parent who reported a history of asthma."

We did not corroborate or confirm the presence of a diagnosis based on source documentation, medical record review, clinical examination or any diagnostic tests. This approach (parental self-report) seems like a reasonable, practical method to determine a parental history of asthma. This approach is also used in everyday practice and would be generalizable to everyday practice, as well.

It is possible that a few parents may have been incorrectly diagnosed with asthma, which would reduce the risk of atopic diseases in their child but, thanks to randomization, would not bias the treatment effect estimates.</td><td>Page 6
Lines 2-3</td><td></td></tr>
<tr><td>A12b. How many parents still had active asthma, doctor-diagnosed asthma, and what was the severity of their asthma?</td><td>The distribution of mothers and fathers who had active, doctor-diagnosed asthma was <u>similar</u> in both the control groups and the intervention groups. Please see the tables below:

Did the Mother Have Active Asthma?
<table>
<tr><th></th><th colspan="3">Active Asthma?</th><th>Mother no asthma</th><th>Mother Data missing</th><th>Total</th></tr>
<tr><th></th><th>Yes</th><th>No</th><th>Unknown</th><th></th><th></th><th></th></tr>
<tr><td>Control</td><td>55</td><td>15</td><td>4</td><td>26</td><td>1</td><td>101</td></tr>
<tr><td>Probiotic</td><td>55</td><td>15</td><td>3</td><td>28</td><td>1</td><td>102</td></tr>
</table>

Did the Father Have Active Asthma?
<table>
<tr><th></th><th colspan="3">Active Asthma?</th><th>Father no asthma</th><th>Father Data missing</th><th>Total</th></tr>
<tr><th></th><th>Yes</th><th>No</th><th>Unknown</th><th></th><th></th><th></th></tr>
<tr><td>Control</td><td>21</td><td>16</td><td>2</td><td>55</td><td>7</td><td>101</td></tr>
</table></td><td>Not applicable</td><td></td></tr>
</table>

Probiotic	32	13	0	51	6	102

The distribution of mothers and fathers who had active asthma (as measured by a recent episode in the last 12 months) was similar in both the control groups and the intervention groups.

Mother with recent episode in last 12 months

	Recent episode in last 12 months?			Mother no asthma	Mother Data Missing
	Yes	No	Unknown		
Control	33	40	1	26	1
Probiotic	38	31	4	28	1

Father with recent episode in last 12 months

	Recent episode in last 12 months?			Father no asthma	Father Data missing
	Yes	No	Unknown		
Control	19	20	0	55	7
Probiotic	22	23	0	51	6

Unfortunately, we did not collect data on the severity of parental asthma.

It is okay to ask the authors to provide additional information; however, make sure that the request is scientifically reasonable

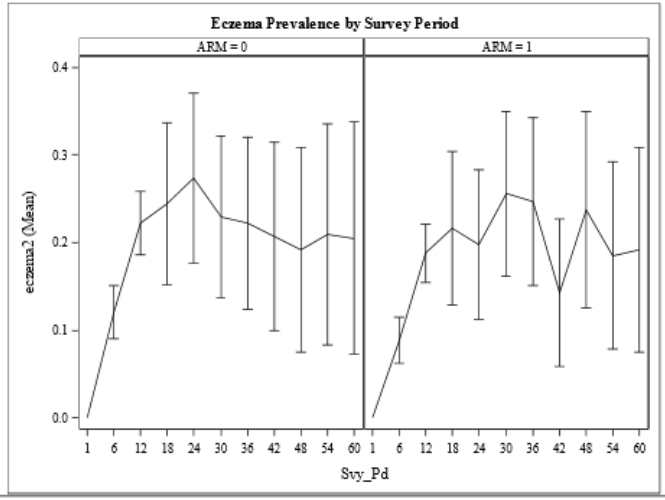
You are asking the authors to do additional work. This request should improve the manuscript

A12c. How many participants had both parents with asthma, and was that similar between the groups? I want to be reassured that enrolled subjects had parents who met firm criteria for having asthma.	There were 30 participants who had both parents with history of asthma. Of those 12 were in the control group and 18 in the probiotic group.	Not applicable

	Which parent had asthma?			Missing	Total
	Mother	Father	Both		
Control	62	26	12	1	101
Probiotic	55	27	18	2	102

In this case no change was made to the final manuscript

A13. The dosing of the probiotics is reasonable and explained in the 2007 publication. However, since most readers will not go back to read the original justification on dosing, it would be good to mention it in the Methods section.	The rationale for the probiotic dose was that it was the same dose used in previous published studies. We added, "This is the same probiotic strain and dose used in two previously published trials.[4,6]"	P Li

	investigate the outcome of active eczema at the given ages of 2, 3, 4, 5 or 6 years? I understand this will decrease sample sizes, but I do think it is an important question to investigate as a secondary analysis.	period. When we compared both the intervention and the control groups, there was no difference in the prevalence of active eczema in both groups throughout the observations periods. The figures below show the prevalence of 'active' eczema. As noted by the reviewer there is some fluctuation after a 'peak' at 2 years of age. Due to the diminishing sample sizes, the confidence intervals are quite wide and it is quite difficult to make any firm conclusions about the change in the prevalence of 'active eczema'.  		
B4.	In the results section numbers mentioned are not in line with numbers in Figure 1. Number of approached is 4382 vs 6457, number of eligible mothers is 218 vs 217. Please clearly explain these differences and avoid confusion.	Thank you for this feedback. In addition, in reviewing the data, we noted there were an additional 19 infants who were randomized; however, the mothers immediately withdrew from the study before the probiotic was ever administered. We corrected the CONSORT chart to correctly state that these infants were randomized. The numbers in the CONSORT chart were corrected.	Page 10 Lines 21-23	
B5.	Could the authors also elaborate on the high percentage of non-eligible mothers? This is 1963 out of 2181 interested mothers (according to text) or 2480	Please see the response to A22 The reviewer is correct that only 8 to 10% of the parents we	Not applicable	

	out of 2697 interested mothers (according to figure 1.). This means that only 8-10% of the total population eligible was for this study. I must assume this is based on the inclusion criterion that father or mother had asthma? If so, how was parental asthma defined; asthma ever, active asthma, ICS use? Are the findings in line with previous reports on asthma prevalence in San Francisco?	screened would be eligible parents for the study. This number is consistent with previous reports on asthma prevalence in the San Francisco area. According to the California Health Interview Survey (CHIS), 2014, the active asthma prevalence is 9.0 (5.9-12.1) for all ages. The lifetime asthma prevalence is 13.2 (9.9-16.6) for all ages. See: http://www.californiabreathing.org/asthma-data/county-asthma-profiles/san-francisco-county-asthma-profile		
5.a.	The strong selection of high-risk children in this study should be more clearly discussed, and it should be stated that results of this study can only be extrapolated to 10% of the total population with (active?) parental asthma. It might be assumed that any effects in lower risk population is even lower, but that remains to some extent speculative.	We agree with this comment and we added this clarification to the limitations section. "Finally, similar to other studies, we recruited high-risk children in this study to increase the likelihood of seeing an effect in the intervention. Although the results of this study can only be extrapolated to those children born to at least one parent with asthma, it is assumed that any effects for lower-risk infants (e.g., infants born to parents without asthma) are probably lower."	Page 15, Line 18-22	
5.b.	In this respect, I find the statements on page 13 lines 53-60 that probiotics may only have an effect in high-risk children not very relevant. The public health impact of any preventive intervention becomes very limited if it may only be effective in a "high risk" subset of an already selected 10% of mothers with the highest baseline risk of asthma based on family history. Literature clearly shows that parental history of asthma is the strongest independent predictor of later asthma at birth, and stronger than breastfeeding, caesarean section or antibiotic use.	We have omitted this statement from the text.	Text removed, as requested.	

Instructions:

Please use this table format to answer the questions posed by the editors and reviewers of your paper. Copy and paste the editor/reviewer's question in the "Comments" column and your answer to that question in the corresponding "Response" column. Be sure to ALSO paste the corrected text along with your response. For minor copyediting changes such as spelling and grammar corrections, you may simply state that the error was corrected, without pasting the altered text.

For clarity, use one row per question. Make sure to list the page and line reference where your change can be found. If no change was made, please make sure to note that in your response in addition to your reasoning. You may delete the sample row and insert rows to this table as needed.

-----Original Message-----
From: onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com
[mailto:onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com]
Sent: Monday, May 01, 2017 9:01 AM
To: Cabana, Michael <Michael.Cabana@ucsf.edu>
Subject: PEDIATRICS: Decision Letter for MS ID 2016-3000.R1

01-May-2017

Manuscript #: 2016-3000.R1

Title: A Randomized Controlled Trial of Early Probiotic Supplementation for Eczema and Asthma Prevention

Type: Regular Article

Dear Dr. Cabana:

The editors of Pediatrics are pleased to report that your manuscript is provisionally accepted for publication. However, we will require additional revisions before a final decision is made. You have 90 (ninety) days to submit a revised paper.

Please respond in detail to the reviewer comments included at the bottom of this e-mail. In addition, please address these items from the editors:

* Change the main title (both in your paper and in online Step 1) to: Early Probiotic Supplementation for Eczema and Asthma Prevention: A Randomized Controlled Trial

* Change the short title (both in your paper and in online Step 1) to: Probiotics for Eczema and Asthma Prevention

Attached, please find a table to use when responding to the comments made by the reviewer(s) and the editors. In addressing any substantive suggestions or criticisms made, please make a numerical listing of the editor/reviewer's question in the first column. Your answer to the question (along with a copy of the corrected text) should be inserted into the corresponding second column, and the page number and paragraph where the change(s) can be found should be inserted into the third column. If no change is made, please note that in the third column.

Once you have completed this table, please upload it as a Supplemental File to your manuscript files. Please keep in mind that if the reviewer's request is for clarification, it should be made in the text of the paper and noted as one of your changes; do not explain your reasoning in the notes to the editors in lieu of making a change in the text.

Your revision should be submitted via http://mc.manuscriptcentral.com/pediatrics. In your Author Dashboard, click on "Manuscripts with Decisions" then create a revision. Please upload the revised version of your manuscript and delete the older version from the system before completing the

submission. The revised manuscript should have no editing tags; it should be an unmarked version without margin notes or boldface notes. Once submitted, your revised manuscript's number will be appended to denote a particular revision (R1, R2, etc).

Your 90-day period for submitting a revised paper begins today. You can monitor the time remaining through your Author Dashboard. If you are unable to resubmit in the time allotted, please contact my office.

We look forward to receiving your revised manuscript.

Sincerely,
Alex R. Kemper, MD, MPH, MS
Deputy Editor, Pediatrics
Duke Clinical Research Institute
2400 Pratt Street, Room 0311 Terrace Level Durham, NC 27710
e-mail: alex.kemper@duke.edu

Reviewer: 1

Comments to the Author:
This is a revised manuscript of a study that evaluated the administration of probiotics in infancy on the development of asthma and eczema. The authors have done an excellent job addressing the reviewers' concerns. The manuscript is well written, the study design sound, and the statistical analysis comprehensive.
One point to consider. The authors found that the cumulative incidence of asthma was 17.4% in the control patient group and 9.7% in the probiotic group. This was not found to be statistically significant. It would be good to include in the discussion why this seemingly large and clinically relevant difference was not found to be statistically significant and whether a large sample size would have been likely to sustain this almost 2-fold difference in cumulative incidence, hence leading to a different interpretation of their results. Also, there is no specific mention of obtaining written informed consent, so that should be clarified. Parental consent is mentioned, but it is not stated that it was written.

Reviewer: 2

Comments to the Author:
Authors have significantly revised their manuscript and have addressed the comments adequately. I think the resulting manuscript would be suitable for publication and I have no further queries.

If the author has addressed all your comments, you don't need to any additional comments

Reviewer #1 brought up two final thoughts regarding the sample size and informed consent.

-----Original Message-----
From: onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com
[mailto:onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com]
Sent: Monday, June 05, 2017 12:54 PM
To: Cabana, Michael <Michael.Cabana@ucsf.edu>; McKean, Michelle <Michelle.McKean@ucsf.edu>; caughey@ohsu.edu; Fong, Lawrence <Lawrence.Fong@ucsf.edu>; Lynch, Susan <Susan.Lynch@ucsf.edu>; Wong, Angela <angela.r.wong@kp.org>; airleong@hotmail.com; Boushey, Homer A <Homer.Boushey@ucsf.edu>; Hoppe, Patricia <Patricia.Hoppe@ucsf.edu>; Hilton, Joan <Joan.Hilton@ucsf.edu>
Subject: PEDIATRICS: Decision Letter for 2016-3000.R2

05-Jun-2017

RE: Manuscript #: 2016-3000.R2

Title: Early Probiotic Supplementation for Eczema and Asthma Prevention: A Randomized Controlled Trial

Authors: Cabana, Michael; McKean, Michelle; Caughey, Aaron; Fong, Lawrence; Lynch, Susan; Wong, Angela; Leong, Russell; Boushey, Homer; Hilton, Joan

Type: Regular Article

Dear Dr. Cabana and colleagues:

The editors of Pediatrics are pleased to accept your article for publication.

You will soon be notified of the issue in which your article is likely to appear. All accepted articles are published online at www.pediatrics.org, which is our journal of record. Our print edition includes abstracts of each article, plus some full articles, the inclusion of which are the sole discretion of the editors. All articles are "early-released" online, usually in the month prior to the official publication date. We will inform you of your anticipated early-release date after the schedule is set.

Page proofs will be sent to you for final review prior to publication. As corresponding author, you will receive these page proofs via email from our printing partner, Dartmouth Journal Services. Given their tight production schedule, there is a *72-hour* turnaround time. Please make arrangements with a co-author if you expect to be unavailable in the near future.

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Going forward, please take great care about communicating any specific content of your article before its publication in Pediatrics, especially to those in the news media or competing journals. Your article is under a strict media embargo until 12:01 a.m. Eastern time on the early-release date. Please keep all editorial correspondence confidential, and refrain from sharing your article's content with anyone who

Early Probiotic Supplementation for Eczema and Asthma Prevention: A Randomized Controlled Trial

Michael D. Cabana, MD, MPH,[a,b,c] Michelle McKean, RD, MPH,[a] Aaron B. Caughey, MD, PhD,[d] Lawrence Fong, MD,[e] Susan Lynch, PhD,[e] Angela Wong, MD,[f] Russell Leong, MD,[g] Homer A. Boushey, MD,[e] Joan F. Hilton, ScD, MPH[b]

abstract

OBJECTIVES: To determine if probiotic administration during the first 6 months of life decreases childhood asthma and eczema.

METHODS: We conducted a randomized, double-blind controlled trial of *Lactobacillus rhamnosus* GG (LGG) supplementation on the cumulative incidence of eczema (primary end point) and asthma and rhinitis (secondary end points) in high-risk infants. For the first 6 months of life, intervention infants ($n = 92$) received a daily dose of 10 billion colony-forming units of LGG and 225 mg of inulin (Amerifit Brands, Cromwell, CT), and control infants ($n = 92$) received 325 mg of inulin alone. We used survival analysis methods to estimate disease incidences in the presence or absence of LGG and to estimate the efficacy of LGG in delaying or preventing these diseases.

RESULTS: Infants were accrued over a 6-year period (median follow-up: 4.6 years; 95% retention rate at 2 years). At 2 years of age, the estimated cumulative incidence of eczema was 30.9% (95% confidence interval [CI], 21.4%–40.4%) in the control arm and 28.7% (95% CI, 19.4%–38.0%) in the LGG arm, for a hazard ratio of 0.95 (95% CI, 0.59–1.53) (log-rank $P = .83$). At 5 years of age, the cumulative incidence of asthma was 17.4% (95% CI, 7.6%–27.1%) in the control arm and 9.7% (95% CI, 2.7%–16.6%) in the LGG arm, for a hazard ratio of 0.88 (95% CI, 0.41–1.87) (log-rank $P = .25$).

CONCLUSIONS: For high-risk infants, early LGG supplementation for the first 6 months of life does not appear to prevent the development of eczema or asthma at 2 years of age.

FREE NIH

Departments of [a]Pediatrics, [b]Epidemiology and Biostatistics, [c]Medicine, and [d]Philip R. Lee Institute for Health Policy Studies, University of California, San Francisco, San Francisco, California; [e]Department of Obstetrics and Gynecology, Oregon Health & Sciences University, Portland, Oregon; [f]Department of Pediatrics, Kaiser Permanente, San Francisco, California; and [g]Department of Pediatrics, California Pacific Medical Center, San Francisco, California

Dr Cabana conceptualized and designed the study, designed the data collection instruments, and drafted the initial manuscript; Ms McKean designed the study, supervised and coordinated the overall data collection, and critically reviewed the manuscript; Drs Caughey, Wong, and Leong supervised the data collection at one of the sites and critically reviewed the manuscript; Drs Fong and Lynch helped design the study and critically reviewed the manuscript; Dr Boushey helped design the study, designed the data collection instruments, and critically reviewed the manuscript; Dr Hilton designed the study analysis plan and critically reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

This trial has been registered at ww.clinicaltrials.gov (identifier NCT00113659).

DOI: https://doi.org/10.1542/peds.2016-3000

Accepted for publication Jun 5, 2017

WHAT'S KNOWN ON THIS SUBJECT: On the basis of the hygiene hypothesis, probiotic exposure may affect immune system development and subsequent risk for allergic disease; however, recent trials of the probiotic *Lactobacillus rhamnosus* GG supplementation in decreasing the risk of childhood eczema and asthma have yielded mixed results.

WHAT THIS STUDY ADDS: For high-risk infants, early *Lactobacillus rhamnosus* GG supplementation does not appear to prevent eczema or asthma development at 2 years of age.

To cite: Cabana MD, McKean M, Caughey AB, et al. Early Probiotic Supplementation for Eczema and Asthma Prevention: A Randomized Controlled Trial. *Pediatrics.* 2017; 140(3):e20163000

Examples of Useful Comments

- It is helpful for the editors to understand how the manuscript fits into the broader literature.

GOOD: "Although the study sample only includes 9 cases, this represents the only collection of pediatric cases reported…"

GOOD: "This is the first report of this particular approach in treating infant botulism…"

GOOD: "These 215 cases of infants with COVID-19 represent the largest report to date…"

GOOD: "This is one of over several dozen surveys on the topic of barriers to physician guideline adherence. It would be helpful if the authors could clarify what is novel in this cross sectional survey. The field is now focused on developing interventions to improve guideline adherence…"

GOOD: "There are already RCTs which have evaluated this therapy in both younger patients and more seriously ill patients. It is not clear how this additional RCT expands what we know about how this therapy can be used…"

- It is helpful for the editors to know if the methods are valid

GOOD: "The use of administrative data from 2010 to 2019 is not appropriate for documenting changes in asthma prevalence based on ICD codes. The ICD codes changed in 2015 and it would be inappropriate to make comparisons with data from 2010-2014 along with data from 2015-2019…"

- It is helpful for the editors to know if the conclusions are valid

GOOD: "This is a cross sectional analysis of BMI data and asthma clinical information. Because the study design is cross sectional, it is not possible infer causality. One cannot conclude that the presence of severe asthma led to obesity or if obesity led to severe asthma.

- Justify your recommendations with specific examples from the manuscript

BAD: "The numbers of patients in results section are not clear…"

GOOD: "In the results section, numbers mentioned are not in line with the numbers in Figure 1. Number of approached is 4382 vs. 6457, number of eligible mothers is 218 vs. 217. Please clearly explain these differences…"

- Be professional and respectful.

BAD: "The manuscript writing is poor. I could barely get through to the end…"

GOOD: "The manuscript could benefit from copyediting and a grammar check. These issues distract from the main content and messages, especially in the discussion section."

- Include any positive comments (especially in the summary paragraph)

GOOD: "The manuscript focuses on an important topic in child health. In addition, there are few papers on the quality of child mental health care in rural areas."

- DO NOT use your review to promote your own work

BAD: "The manuscript does not reference a similar but important study by Smith, et al. (2012). Although the focus of the Smith study is different, the methodology can be applied to this current study."

- DO NOT focus on typographical errors

NOT VERY HELPFUL: "The use of a semicolon on page 12, line 3 would be much more effective…"

What is a Minor Issue?

- Reference listed is incomplete
- Data presentation (e.g., authors included p values, but not confidence intervals)
- Technical question about a specific part of the methods (e.g., what was the specific brand of the reagent or antigen)
- Typographical mistakes
- Confusing sentences

You are a reviewer of a manuscript and you don't understand a key paragraph in the results section. What should you do?

A. Write an email to the author of the manuscript.
B. Write an email to the editor of the journal and describe the issue.
C. Include a comment that a key paragraph in the results section is unclear in your review
D. Ask a colleague to read the paragraph and obtain their opinion and interpretation of the paragraph

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C. Include a comment that a key paragraph in the results section is unclear in your review

D. Ask a colleague to read the paragraph and obtain their opinion and interpretation of the paragraph

You cannot disclose information from a manuscript that is undergoing peer-review to a colleague

What is a masked review?

A. When you have to wear an N95 mask while you review a manuscript
B. When you have to wear a Halloween mask while you review a manuscript
C. When the name of the authors are removed from the title page
D. None of the above

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A. When you have to wear an N95 mask while you review a manuscript

B. When you have to wear a Halloween mask while you review a manuscript

C. When the name of the authors are removed from the title page

D. None of the above

Proper "Masking" of a Manuscript

- Name of the authors are redacted from the title page
- Name of the institution is redacted from the title page as well as in any section of the manuscript
- The description of the setting of the study may also have to be redacted from the text (e.g., "a large children's hospital located in the Bronx")

Some journals may ask you to review a 'masked' manuscript. Regardless of whether or not the manuscript is 'masked', you should not be biased by the author or the institutions represented.

Does masking a manuscript lead to higher quality reviews?

A. We don't know. There are no randomized controlled trials on this topic.
B. No, manuscripts of well-known authors are difficult to mask
C. Yes, masking saves time for the reviewers
D. Yes, masking helps get rid of any implicit bias with the reviewers

Does masking a manuscript lead to higher quality reviews?

A. We don't know. There are no randomized controlled trials on this topic.

B. No, manuscripts of well-known authors are difficult to mask

C. Yes, masking saves time for the reviewers

D. Yes, masking helps get rid of any implicit bias with the reviewers

Does Masking Author Identity Improve Peer Review Quality?

A Randomized Controlled Trial

Amy C. Justice, MD, PhD; Mildred K. Cho, PhD; Margaret A. Winker, MD; Jesse A. Berlin, ScD; Drummond Rennie, MD; and the PEER Investigators

Context.—All authors may not be equal in the eyes of reviewers. Specifically, well-known authors may receive less objective (poorer quality) reviews. One study at a single journal found a small improvement in review quality when reviewers were masked to author identity.

Objectives.—To determine whether masking reviewers to author identity is generally associated with higher quality of review at biomedical journals, and to determine the success of routine masking techniques.

Design and Setting.—A randomized controlled trial performed on external reviews of manuscripts submitted to *Annals of Emergency Medicine, Annals of Internal Medicine, JAMA, Obstetrics & Gynecology*, and *Ophthalmology*.

Interventions.—Two peers reviewed each manuscript. In one study arm, both peer reviewers received the manuscript according to usual masking practice. In the other arm, one reviewer was randomized to receive a manuscript with author identity masked, and the other reviewer received an unmasked manuscript.

Main Outcome Measure.—Review quality on a 5-point Likert scale as judged by manuscript author and editor. A difference of 0.5 or greater was considered important.

Results.—A total of 118 manuscripts were randomized, 26 to usual practice and 92 to intervention. In the intervention arm, editor quality assessment was complete for 77 (84%) of 92 manuscripts. Author quality assessment was complete on 40 (54%) of 74 manuscripts. Authors and editors perceived no significant difference in quality between masked (mean difference, 0.1; 95% confidence interval [CI], −0.2 to 0.4) and unmasked (mean difference, −0.1; 95% CI, −0.5 to 0.4) reviews. We also found no difference in the degree to which the review influenced the editorial decision (mean difference, −0.1; 95% CI,−0.3 to 0.3). Masking was often unsuccessful (overall, 68% successfully masked; 95% CI, 58%-77%), although 1 journal had significantly better masking success than others (90% successfully masked; 95% CI, 73%-98%). Manuscripts by generally known authors were less likely to be successfully masked (odds ratio, 0.3; 95% CI, 0.1-0.8). When analysis was restricted to manuscripts that were successfully masked, review quality as assessed by editors and authors still did not differ.

Conclusions.—Masking reviewers to author identity as commonly practiced does not improve quality of reviews. Since manuscripts of well-known authors are more difficult to mask, and those manuscripts may be more likely to benefit from masking, the inability to mask reviewers to the identity of well-known authors may have contributed to the lack of effect.

JAMA. 1998;280:240-242

IT HAS BEEN suggested that masking reviewers to author identity would improve the fairness and the quality of peer review[1] because well-known authors' work may be reviewed less critically. Yet only a small fraction of journals routinely mask reviewers.[2,3] When editors are asked why they do not mask, they cite an "overwhelming burden" associated with masking.[2,3] Some question whether it is possible to mask successfully.[2,4]

One study, conducted at a single journal,[5] demonstrated that the quality of masked reviews was statistically higher than that of unmasked reviews, although that difference was small. We tested the hypothesis that masking peer reviewers to author identity improves the quality of peer review at 5 biomedical journals. To increase the generalizability of our study, we used a masking procedure that is commonly practiced.

METHODS

Journals

Five journals participated in the study: *Annals of Emergency Medicine, Annals of Internal Medicine, JAMA, Obstetrics & Gynecology*, and *Ophthalmology*. Only 1 of these journals, *Annals of Emergency Medicine*, routinely masks reviewers to author identity.

Manuscript Enrollment

Eligible manuscripts were submitted between November 1995 and March 1996 and met the following inclusion criteria: (1) the manuscript reported original research, including meta-analyses

Justice AC, Cho MK, Winker MA, Berlin JA, Rennie D. Does masking author identity improve peer review quality? A randomized controlled trial. PEER Investigators [published correction appears in JAMA 1998 Sep 16;280(11):968]. *JAMA*. 1998;280(3):240-242. doi:10.1001/jama.280.3.240

Summary

- Peer review is an important part of the scientific process and an important way that you participate in the scientific community
- Providing a thoughtful and thorough peer-review of a manuscript can help you be a better writer
- Your review will include comments to the author and separate comments to the editor
- The most important task is for you to comment on the validity, quality and originality of a potential article for publication

Summary

- Be professional and respectful
- Be specific with your comments
- Be helpful and constructive, when possible
- Don’t promote your own work
- Don’t break confidentiality
- Submit your reviews on time

Questions?