

## 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>	Does Macrolide use confer risk of out-of-hospital cardiac arrest compared with penicillin-V?: a Danish national case-crossover and case-time-control study
<b>AUTHORS</b>	Hertz, F; Jensen, Aksel; Dahl Knudsen, Jenny; Arpi, Magnus; Andersson, Charlotte; Gislason, Gunnar; Køber, Lars; Torp-Pedersen, Christian; Lippert, Freddy; Weeke, Peter

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Sam Doerken Institute for Medical Biometry and Statistics Faculty of Medicine and Medical Center – University of Freiburg
<b>REVIEW RETURNED</b>	19-Oct-2017

<b>GENERAL COMMENTS</b>	<p>I am only commenting on the statistics of the article.</p> <p>Short answer: The methods are adequate and described sufficiently.</p> <p>Long answer: I'm happy to see the case-crossover design applied, it seems very appropriate for this setting. The authors mention that it applies to events with an acute onset and that it controls for time-invariant confounding. The case period, reference period and washout period are all defined. The number of discordant pairs are reported, making the study somewhat reproducible. Confidence intervals are given precedence over p-values. Another strength are the sensitivity analyses in varying the different period lengths and considering different populations. STROBE guidelines are effectively employed.</p> <p>I'm sorry that I don't have any constructive points - this may please or displease the authors.</p>
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<b>REVIEWER</b>	Joshua Reynolds, MD, MS Michigan State University College of Human Medicine; United States
<b>REVIEW RETURNED</b>	10-Nov-2017

<b>GENERAL COMMENTS</b>	The authors performed a case-crossover and case-time-control study to evaluate for increased risk of OHCA in subjects treated with a course of macrolides compared to penicillin.
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	<p>This is an interesting take on this question, given the described conflicting evidence to date.</p> <p>Overall, the study design and methodology appears robust, and the manuscript is organized and clearly written. I have only a few suggestions/considerations for the authors.</p> <p>1) My primary concern is about case ascertainment – I wonder if the authors may have missed deaths since this analysis is restricted to subjects in the national cardiac arrest registry, which predicated attempted resuscitation. Is there a national death database that could be queried to check for deaths without attempted resuscitation?</p> <p>2) Final paragraph of the Introduction. Great summary of the aims and preview of the study design. Is there a particular hypothesis?</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Sam Doerken

Institution and Country: Institute for Medical Biometry and Statistics, Faculty of Medicine and Medical Center – University of Freiburg

Please state any competing interests: None declared

Please leave your comments for the authors below  
I am only commenting on the statistics of the article.

Short answer:

The methods are adequate and described sufficiently.

Long answer:

I'm happy to see the case-crossover design applied, it seems very appropriate for this setting. The authors mention that it applies to events with an acute onset and that it controls for time-invariant confounding. The case period, reference period and washout period are all defined.

The number of discordant pairs are reported, making the study somewhat reproducible. Confidence intervals are given precedence over p-values.

Another strength are the sensitivity analyses in varying the different period lengths and considering different populations. STROBE guidelines are effectively employed.

Comment: I'm sorry that I don't have any constructive points - this may please or displease the authors.

Response: We appreciate the thorough review of the statistical method of the manuscript made by the reviewer. We are very pleased that the statistical methods are adequately and sufficiently described.

Reviewer: 2

Reviewer Name: Joshua Reynolds, MD, MS

Institution and Country: Michigan State University College of Human Medicine; United States  
 Please state any competing interests: None declared

Please leave your comments for the authors below

The authors performed a case-crossover and case-time-control study to evaluate for increased risk of OHCA in subjects treated with a course of macrolides compared to penicillin. This is an interesting take on this question, given the described conflicting evidence to date.

Overall, the study design and methodology appears robust, and the manuscript is organized and clearly written. I have only a few suggestions/considerations for the authors.

1) My primary concern is about case ascertainment – I wonder if the authors may have missed deaths since this analysis is restricted to subjects in the national cardiac arrest registry, which predicated attempted resuscitation. Is there a national death database that could be queried to check for deaths without attempted resuscitation?

Response: We agree with the reviewer that there is a possibility that individuals with no attempt of resuscitation may have suffered from a cardiac arrest. Currently, patients with obvious signs of death (e.g., trauma or rigor mortis), and for whom no resuscitative efforts were performed by bystanders or EMS personnel, were excluded from the Danish Cardiac Arrest Registry. We acknowledge that while this approach is likely to increase the sensitivity of the registry, specificity may be the trade-off. We have added this as a limitation.

Revised manuscript (page 15, lines 351-354): We also acknowledge that patients in which no resuscitative efforts were performed or patients with obvious signs of death may indeed have suffered from a cardiac arrest, but have been excluded from the Danish Cardiac Arrest Registry.

2) Final paragraph of the Introduction. Great summary of the aims and preview of the study design. Is there a particular hypothesis?

Response: We thank the reviewer for his comments. Given the conflicting results previously on macrolides and cardiovascular mortality, the null hypothesis was that no difference between macrolide and penicillin-V and association with out-of-hospital cardiac arrest could be identified. Due to the mentioned conflicting results, we would prefer not to state the null hypothesis in the introduction and keep the summary of the aims. We hope the reviewer can agree with this decision.

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Joshua C. Reynolds, MD, MS Michigan State University College of Human Medicine. United States.
<b>REVIEW RETURNED</b>	12-Dec-2017
<b>GENERAL COMMENTS</b>	The authors have satisfied my Reviewer Comments.