

Peer Review File

Article information: <https://dx.doi.org/10.21037/fomm-23-18>

Reviewer A

Comment 1: The authors have done well to do a well researched study on animal inflicted injuries. They highlight a commonly encountered problem seen in emergency rooms and do provide some guidelines on rational use of antibiotics. The emphasis on adequate irrigation and keeping the time of injury in mind before deciding will also help residents as they manage these injuries. I would recommend adding a flow chart / decision tree which should focus on different variables affecting decision (time elapsed, animal - cat/dog, patient's immune status, type of wound - puncture?)

Reply 1: We attempted to create a graph to facilitate decision-making, but all images were inferior to Table 3, where prophylaxis is mandatory for high-risk cases (right) and not indicated for low-risk cases (left).

Reviewer B

The authors present the findings of their meta-analysis in a manuscript titled “Antibiotic prophylaxis for animal inflicted maxillofacial injuries: a systematic review and meta-analysis”. In this analysis, the efficacy of prophylactic antibiotics in the treatment of animal bites in the face and scalp is examined with a meta-analysis of the current literature.

Abstract: The abstract is concise and provides a comprehensive overview of the review's key points.

Comment 2: Introduction: The introduction initially lists a wide range of living creatures, including scorpions (which, to the best of my knowledge, do not bite), and other animals that did not meet the inclusion criteria for the analysis. While these may be mentioned in the literature reviewed, they are not relevant to establishing the purpose of the article. An introduction should provide a logical progression explaining the rationale for the use or non-use of antibiotic prophylaxis for animal bites. Although the authors present prior reports and articles, the middle portion of the introduction simply states that antibiotic prophylaxis is indicated, which contradicts the overall aim of the review, namely does it or does it not prevent infections. The authors should also clearly state their hypothesis or null-hypothesis.

Reply 1: Massive change in the abstract was performed.

Changes in the text: An estimated 4.5 million dog bites occur across America each year (1). Bears, wild boars, snakes, leopards, crocodiles, and a variety of animals besides domestic ones have been reported to cause injuries. The number of attacks from wild animals is increasing and the main

reason is human spread through wild areas (2). The social distancing measures during the pandemic have also significantly increased the number of attacks from domestic animals (3). Head and neck suffer more of these injuries because the maxillofacial region has a prominent anatomical position. It is estimated that 1% of all emergency room visits across the globe are due to animal bites (4). The overall range is hard to calculate due to the fact such a lot of attacks go unreported, however with this simple calculation it is possible to see the significance of animal attack management on the face. Human bites have to be additionally be a topic of research because the annual count is alarmingly growing (5,6).

Comment 3: Methods and Materials: The methodology and article selection process appear to be well-designed and accurately implemented. However, I have a critique regarding the inclusion of mammals, avian, reptiles, and insects all in the same data pool. In this reviewer's opinion, these represent different clinical situations and should not be analyzed together, especially considering that 80%-90% of the reported bites were from dogs. It would be more advantageous for the authors to limit their analysis to dog bites in order to draw more meaningful clinical conclusions.

Reply 1: We fully understand this issue, but limiting the study to dog bites would hinder the creation of an antibiotic prophylaxis guide for all cases of animal bites. Although there were few reports, the included articles made it possible to create this table. Changes in the materials and methods section in this regard would render both the table and the article meaningless.

Comment 4: Results: The authors present their results in a manner more akin to a literature review rather than a meta-analysis. They should present their findings in a pooled fashion, highlighting the differences observed in each study. Some authors present data directly correlating to the hypothesis of the analysis. The weaknesses or confounders of the included articles can be discussed in the subsequent section.

Reply 1: Two paragraphs were changed to highlight meta-analysis discussion

Changes in the text: A forest plot was created using RevMan 5.4 to evaluate the Risk Ratio of the included articles concerning the association between wound infection and antibiotic prophylaxis (Figure 2). The analysis indicated that the risk of wound infection was similar in both the antibiotic prophylaxis group and the control group, with a slightly higher but not statistically significant risk difference (RD) of 0.01 (95% CI -0.02-0.05, P = 0.40). The assessment of heterogeneity revealed moderate evidence of variability among the studies (P = 0.05, I² = 45%). To perform the meta-analysis, the fixed-effects model was employed.

A funnel plot was constructed to visualize the studies comparing antibiotic prophylaxis (Figure 4). It was observed that two studies (24,27) fell outside the boundaries of the funnel plot. This deviation can be attributed to the larger sample sizes in these studies compared to others. In order

to further investigate the potential publication bias, Egger's test was conducted, yielding a value of 5.2875 (95% CI = -10.6200 to 21.3276) with a significant p-value of less than 0.0001. This significant asymmetry between studies indicates a high risk of bias in the publication of these studies. Egger's test is a statistical analysis used to assess the presence of publication bias in research studies.

Comment 5: Discussion: The discussion raises concerns about antibiotic resistance. It would be interesting if the authors presented current data on the prevalence of antibiotic resistance in the listed microbes. This secondary purpose, related to antibiotic resistance, should be clearly delineated from the primary aim of determining the need for antibiotic prophylaxis in managing animal bites.

Reply 1: One paragraph was added to discussion session.

Changes in the text: The increasing bacterial resistance observed in bacteria such as Streptococcus, E. coli, Pasteurella, Prevotella, and Bacteroides emphasizes the critical importance of avoiding the overuse of antibiotic prophylaxis. Overuse and misuse of antibiotics can lead to the emergence of resistant strains, rendering these medications ineffective in combating infections. Antibiotic resistance is a global public health concern that threatens our ability to effectively treat bacterial infections. By practicing appropriate antibiotic stewardship, healthcare professionals can help preserve the efficacy of antibiotics for future generations. This entails using antibiotics judiciously, only when necessary, and adhering to evidence-based guidelines for antibiotic prophylaxis. It is vital to weigh the potential benefits against the risks of antibiotic use, considering the individual patient's condition and the specific circumstances of the procedure or injury. Furthermore, implementing comprehensive infection control measures, promoting vaccination, and exploring alternative strategies to prevent infections can all contribute to reducing the reliance on antibiotics and mitigating the development of bacterial resistance. By adopting a multidisciplinary approach and working collaboratively, healthcare providers, researchers, policymakers, and the public can collectively address the challenge of antibiotic resistance and safeguard the effectiveness of these life-saving medications.

Comment 6: The authors appropriately acknowledge the limitations of their analysis, which are accurate. The statement that a definitive conclusion could not be reached should be the final statement, as it is interesting and aligns with their list of identified limitations. Furthermore, it is evident that further studies should be conducted to address these limitations.

Reply 1: "definitive conclusion" was added to the conclusion session.

Changes in the text: According to the available literature this systematic review has demonstrated no definitive conclusion on whether or not antibiotic prophylaxis should be given or not to patients with animal bites (RD 0.01). Antibiotic prophylaxis should be earned in high-risk cases. The cost-

benefit of growing bacterial resistance needs to be appraised. Studies with a lower risk of bias are required on this topic.

We would like to thank the authors for this submission of this interesting topic.

Reviewer C

Comment 7: This is a topic of potential interest to our readers, however, the conclusions derived from the systematic review has demonstrated no clear outcome on whether or not antibiotic prophylaxis should be given or not to patients with animal bites. This conclusion provides no new information or clinical guidance and would not recommend publication.

Reply 1: changes were performed in the conclusion session. The urgent need for more conclusive and low bias articles is needed. With available scientific information there is no possibility to draw a clinical guidance.

Changes in the text: According to the available literature this systematic review has demonstrated no definitive conclusion on whether or not antibiotic prophylaxis should be given or not to patients with animal bites (RD 0.01). Antibiotic prophylaxis should be earned in high-risk cases. The cost-benefit of growing bacterial resistance needs to be appraised. Studies with a lower risk of bias are required on this topic.

Re-review Comments

Reviewer A

The authors have done well to incorporate the changes and that has made the article more succinct and highlights the important points well.

Reviewer B

The authors resubmitted their manuscript titled “Antibiotic prophylaxis for animal inflicted maxillofacial injuries: a systematic review and meta-analysis”.

The authors rewrote many parts of this manuscript, following the reviewers suggestions. The abstract is now consistent with the main article but remaining concise in it’s word count. The introduction is more sequenced and now addresses the purpose of the article, does the literature support the prophylactic administration of antibiotics for animal bites. The purpose is clear.

I was happy to see that the authors included an Egger’s test since this is very appropriate and necessary for this particular analysis.

The discussion is more focused on their findings. Their final conclusion is that there is not enough solid evidence to make a determination is telling. The authors show that there is a hole in our understandings on how to manage a very common occurrence.