

## Article processing charge for manuscript submitted to BMC Infectious Diseases

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The first line antibiotics susceptibility pattern of toxigenic *Corynebacterium diphtheriae* in Indonesia  
Dominicus Husada, Sugi Deny Pranoto, Indra Suwarin Kurniawati, Adi Pramono Hendrata, Eveline Irawan, Leny  
Kartina, Dwiyanti Puspitasari, Parwati Setiono Basuki and Ismoedijanto Moedjito  
BMC Infectious Diseases

Dear Mr husada

Thank you for agreeing the article processing charge for BMC Infectious Diseases. I would like to update you regarding your status with respect to the article processing charge that is normally due if a manuscript is accepted.

You have agreed to pay an article processing charge of GBP 1,192.00/USD 1,752.00/EUR 1,432.00 if your manuscript is accepted. Since you are based in Indonesia, you will be charged the price of EUR 1,432.00.

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## Confirmation of your submission to BMC Infectious Diseases - INFD-D-19-01788

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INFD-D-19-01788

The first line antibiotics susceptibility pattern of toxigenic *Corynebacterium diphtheriae* in Indonesia  
Dominicus Husada, MD, PhD; Sugi Deny Pranoto, MD, Pediatrician; Indra Suwarin Kurniawati, Bachelor; Adi Pramono  
Hendrata, MD; Eveline Irawan, MD; Leny Kartina, MD, Pediatrician; Dwiyantri Puspitasari, MD, Pediatrician; Parwati  
Setiono Basuki, Profesor, MD, Pediatrician; Ismoedijanto Moedjito, Profesor, MD, Pediatrician  
BMC Infectious Diseases

Dear Mr Husada,

Thank you for submitting your manuscript 'The first line antibiotics susceptibility pattern of toxigenic *Corynebacterium diphtheriae* in Indonesia' to BMC Infectious Diseases.

The submission id is: INFD-D-19-01788

Please refer to this number in any future correspondence.

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## AU - Author Information about Handling Editor

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To: dominicushusada@yahoo.com

Date: Tuesday, 17 September 2019, 04:54 pm GMT+7

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The first line antibiotics susceptibility pattern of toxigenic *Corynebacterium diphtheriae* in Indonesia  
Dominicus Husada, MD, PhD; Sugi Deny Pranoto, MD, Pediatrician; Indra Suwarin Kurniawati, Bachelor; Adi Pramono  
Hendrata, MD; Eveline Irawan, MD; Leny Kartina, MD, Pediatrician; Dwiyanti Puspitasari, MD, Pediatrician; Parwati  
Setiono Basuki, Profesor, MD, Pediatrician; Ismoedijanto Moedjito, Profesor, MD, Pediatrician  
BMC Infectious Diseases

Dear Mr Husada,

To update you on your submission's status, your manuscript is being handled through peer review by Dr. Peter Daley who is the Handling Editor of your manuscript.

Your manuscript: "The first line antibiotics susceptibility pattern of toxigenic *Corynebacterium diphtheriae* in Indonesia"

BMC Journal: BMC Infectious Diseases

If you have any queries, please use the 'CONTACT US' link to get in touch with the Journal Editorial Office or 'Send E-mail' from your Action links.

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## Your submission to BMC Infectious Diseases - INFD-D-19-01788

From: BMC Infectious Diseases Editorial Office (em@editorialmanager.com)

To: dominicushusada@yahoo.com

Date: Tuesday, 8 October 2019, 02:39 am GMT+7

INFD-D-19-01788

The first line antibiotics susceptibility pattern of toxigenic *Corynebacterium diphtheriae* in Indonesia  
Dominicus Husada, MD, PhD; Sugi Deny Pranoto, MD, Pediatrician; Indra Suwarin Kurniawati, Bachelor; Adi Pramono  
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Setiono Basuki, Profesor, MD, Pediatrician; Ismoedijanto Moedjito, Profesor, MD, Pediatrician  
BMC Infectious Diseases

Dear Mr Husada,

Your manuscript "The first line antibiotics susceptibility pattern of toxigenic *Corynebacterium diphtheriae* in Indonesia" (INFD-D-19-01788) has been assessed by our reviewers. They have raised a number of points which we believe would improve the manuscript and may allow a revised version to be published in BMC Infectious Diseases.

Their reports, together with any other comments, are below. Please also take a moment to check our website at <https://www.editorialmanager.com/infid/> for any additional comments that were saved as attachments.

If you are able to fully address these points, we would encourage you to submit a revised manuscript to BMC Infectious Diseases.

Once you have made the necessary corrections, please submit online at:

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Please include a cover letter with a point-by-point response to the comments, describing any additional experiments that were carried out and including a detailed rebuttal of any criticisms or requested revisions that you disagreed with. Please also ensure that all changes to the manuscript are indicated in the text by highlighting or using track changes.

Please also ensure that your revised manuscript conforms to the journal style, which can be found at the Submission Guidelines on the journal homepage.

A decision will be made once we have received your revised manuscript, which we expect by 06 Nov 2019.

Please note that you will not be able to add, remove, or change the order of authors once the editor has accepted your manuscript for publication. Any proposed changes to the authorship must be requested during peer-review, and adhere to our criteria for authorship as outlined in BioMed Central's policies. To request a change in authorship, please download the 'Request for change in authorship form' which can be found here - <http://www.biomedcentral.com/about/editorialpolicies#authorship>. Please note that incomplete forms will be rejected. Your request will be taken into consideration by the editor, and you will be advised whether any changes will be permitted. Please be aware that we may investigate, or ask your institute to investigate, any unauthorized attempts to change authorship or discrepancies in authorship between the submitted and revised versions of your manuscript.

I look forward to receiving your revised manuscript and please do not hesitate to contact us if you have any questions.

Best wishes,

Peter Daley, MD MSc FRCPC DTM+H  
BMC Infectious Diseases  
<https://bmcinfectdis.biomedcentral.com/>

**Technical Comments:****Editor Comments:**

Thanks for submitting to BMC Infectious Diseases. The topic is of interest, as there are few published reports. The manuscript needs a lot of improvement, as the three reviewers have outlined. The interpretations will need to be re-analyzed using recent breakpoints. If the authors choose to resubmit, significant revision will be required before acceptance.

Further to the reviewer's suggestions, I add the following:

Please explain further how a sample size of 104 cultures was calculated.  
Provide details on the laboratory's international accreditation status.

BMC Infectious Diseases operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

**Reviewer reports:**

Anusak Kerdsin (Reviewer 1): The manuscript is very interesting for antimicrobial susceptibility on diphtheria pathogen in developing country. There are very few data from this region. However, I have some comments to authors to improve their manuscript.

1. The major disadvantage of this article is the old version of CLSI M45, 2010 used for interpretation. Right now, the current version of CLSI is M45, 3rd edition, 2015. I strongly recommend to use this update version (CLSI M45, 2015) for interpret MIC value. Due to MIC of penicillin was changed in this current version ( $\leq 0.12$  is susceptible; 0.25-2 is intermediate;  $\geq 4$  is resistance). Therefore, interpretation results of MIC for penicillin should be revised all.
2. Interpretation of MIC for oxacillin using interpretative referred to CLSI-M100 *Staphylococcus* spp. is not accepted because there are different species, mechanisms, susceptibility and MIC value may be different. I recommend the authors should separate oxacillin MIC to another Table and show only MIC value.
3. As same as oxacillin MIC, azithromycin and clarithromycin have no interpretation in the current M45 (2015). MIC of erythromycin might be used to interpret these antimicrobial agents due to they are same group. However, I would like to recommend the authors to show the MIC value of azithromycin and clarithromycin too.
4. The current version of CLSI M45, 3rd, 2015, should be used as reference and referred. Authors should refer this one in the reference.
5. Line 124, the authors specify as "104", but in line 167 specify "114", which one is correct?
6. Percentage (%) should be shown in line 172 "...were mitis (...%); line 177 "...were penicillin (...%), clarithromycin (...%), and erythromycin (...%)." .
7. Line 174-177, MIC range of susceptible, intermediate, and resistance should be described for tested isolates.
8. Line 241 - 242, Eighteen point five percent .....should be rewritten for smooth reading such as "Twenty isolates (18.5%; 20/108) have lower susceptibility..."
9. Line 276, "Eighty-eight point nine percent ....." should be reword as same as no.8.
10. Table 1 is no need. Authors can omit it due to this should be referred to CLSI.
11. Please check Table 2. for number and percent of *gravis*, *mitis* *intemedius*, *befanti*
12. Table 3., Interpret of oxacillin should be removed. This should separate to a new Table and show only MIC value.
13. MIC value of azithromycin and clarithromycin should be shown in the same Table of oxacillin.

14. Footnote of interpretation for MIC in Table 3. should be changed. CLSI M100 could be deleted.

15. Paveenkittiporn W, et al., Molecular epidemiology and antimicrobial susceptibility of outbreak-associated *Corynebacterium diphtheriae* in Thailand, 2012. *Infect Genet Evol.* 2019 Aug28;75:104007. doi: 10.1016/j.meegid.2019.104007, may be useful for authors in part of discussion. This paper used the criteria of MIC from the current version of M45, 2015.

Sylvain Brisse (Reviewer 2): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format. Please overwrite this text when adding your comments to the authors.

The manuscript present important, fresh data on susceptibility of *C. diphtheriae* strains to a few but important antimicrobial agents: penicillins and macrolides. The data produced is novel, interpreted according to defined criteria, and valuable.

I have, however, some reservations about the manuscript in its present form.

First the Results section is very short and could be extended by providing more details on the data. I would suggest to present a histogram of MIC values for each antimicrobial agent as a novel figure. This would help future studies to evaluate their work compared to this one. Also, you could show Mitis and Gravis biovars in different colors on the same graph for example.

Also important, please provide a single (supplementary) table with all provenance and microbiological data for each isolate compiled here. It is important to provide the raw data in an open data perspective so that other researchers interested in susceptibility of *C. diphtheriae* could evaluate the data and reuse it. To some extent, the tables are already provided, but please reformat into a more classical tabulated table comprising all the information - I was not able to understand several supplementary materials.

Next, there is some ambiguity about penicillin non-susceptible isolates. Sometimes you consider them intermediate (abstract, 3.7%), sometimes resistant (line 178) and sometimes susceptible (line 292 and even in abstract, conclusion sentence). Please harmonize and decide how to consider the three intermediates.

Fourth, the English language do need attention. Please make it proof read.

Five, I would suggest it could be interesting to provide 2D plots of the correlation between MICs of some agents, for example the distinct macrolides. It could be interesting to detail whether the same isolates were resistant to different macrolides.

Six, it is important to clarify that several authors used different breakpoints to define resistance. For example, I would be surprised if the Brazilian studies quoted by the authors have used the same breakpoint for penicillin as other quoted studies. The authors should detail for each of the reported work, whether the breakpoint was typical or quite different, possibly leading artificially to very different rates of resistance.

Can you comment on antidiphtheria serum availability in your region?

You use the term 'outbreak' several times, but is it really an outbreak in the epidemiological sense? Is it not rather, endemicity background? Please explicit your definition of outbreak.

Line 133: 'screening': what is it?

Line 153: you use erythromycin criteria to interpret azithromycin. How OK is this, is it common practice?

Ethical clearance: why did you need one? Analysis of bacterial strains does not require this in principle.

Line 227: what is meant by "MIC < 0.002; 0.38 ug/ml" ?

Line 228: how many would be non-susceptible in Brazil with your own cutoff?

Same on line 231 for Indian isolates and line 244 and 261; how many would be resistant with your cutoff?

Line 238: tolerance: what do you mean, resistance, non-susceptibility?

Line 269: is it really mutations, or rather acquisition of ermX gene?

Line 273: "ere": please double check

Line 285: multiresistant: again, please check/discuss breakpoints used.

Please replace 'sensible' by 'susceptible' everywhere.

Table 1: first and last columns not useful

Table 2: there is a shift of line for the biovars it seems

Table 3: susceptible, not sensitive

0,5 should be 0.5

Samir Patel (Reviewer 3): This manuscript describes susceptibility profiles of *C. diphtheriae* isolates collected from East Java from 2012-17. The susceptibility testing was carried out using a gradient method, which is not a reference method recommended by the CLSI. The manuscript needs significant revision including discussing the impact/relevance of the results into the broader context.

Major comments:

- \* Overall, the manuscript needs to be revised and revised by someone who is fluent in English.
- \* The authors used erythromycin MIC criteria to interpret both azithromycin and clarithromycin. There is no reference and evidence to suggest that this is accurate. This needs to be explained with appropriate references.
- \* It is not clear why oxacillin breakpoints were used as aminopenicillins are not routinely used to treat *C. diphtheriae*
- \* Lines 212-218: Not sure why this information is stated. It is not related to the paper
- \* The authors reported that only 53.7% of the isolates were susceptible to oxacillin, whereas 96.3% of isolates were susceptible to penicillin. The manuscript doesn't address the reasons behind the high discrepancy between these antibiotics.
- \* Similarly, the authors fail to discuss the difference in susceptibility results among macrolides

Minor comments:

- \* Lines 83 and 87: Consider revising this statement using proper English language
- \* Should use male and female rather than boys and girls
- \* Line 177-180 is not clear.

If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service ([http://bit.ly/NRES\\_BS](http://bit.ly/NRES_BS)) and American Journal Experts ([http://bit.ly/AJE\\_BS](http://bit.ly/AJE_BS)) for help with English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial (<https://www.springer.com/gb/authors-editors/authorandreviewertutorials/writinginenglish>) and our Writing resources (<http://www.biomedcentral.com/getpublished/writing-resources>). These cover common mistakes that occur when writing in English.

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For the 'Availability of data and materials' section, please provide information about where the data supporting your findings can be found. We encourage authors to deposit their datasets in publicly available repositories (where available and appropriate), or to be presented within the manuscript and/or additional supporting files. Please note that identifying/confidential patient data should not be shared. Authors who do not wish to share their data must confirm this under this sub-heading and also provide their reasons. For further guidance on how to format this section, please refer to BioMed Central's editorial policies page (see links below).

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- Ethics approval and consent to participate
- Consent to publish
- Availability of data and materials
- Competing interests
- Funding
- Authors' Contributions
- Acknowledgements

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INFD-D-19-01788R1

First-line antibiotics susceptibility pattern of toxigenic *Corynebacterium diphtheriae* in Indonesia  
Dominicus Husada, MD, PhD; Sugi Deny Pranoto, MD, Pediatrician; Indra Suwarin Kurniawati, Bachelor; Adi Pramono  
Hendrata, MD; Eveline Irawan, MD; Leny Kartina, MD, Pediatrician; Dwiyantri Puspitasari, MD, Pediatrician; Parwati  
Setiono Basuki, Profesor, MD, Pediatrician; Ismoedijanto Moedjito, Profesor, MD, Pediatrician  
BMC Infectious Diseases

Dear Mr Husada,

Thank you for the revised version of your manuscript 'First-line antibiotics susceptibility pattern of toxigenic *Corynebacterium diphtheriae* in Indonesia' submitted to BMC Infectious Diseases.

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INFD-D-19-01788R3

First-line antibiotics susceptibility pattern of toxigenic *Corynebacterium diphtheriae* in Indonesia  
Dominicus Husada, MD, PhD; Sugi Deny Pranoto, MD, Pediatrician; Indra Suwarin Kurniawati, Bachelor; Adi Pramono Hendrata, MD; Eveline Irawan, MD; Leny Kartina, MD, Pediatrician; Dwiyantri Puspitasari, MD, Pediatrician; Parwati Setiono Basuki, Profesor, MD, Pediatrician; Ismoedijanto Moedjito, Profesor, MD, Pediatrician  
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## Confirmation of revised submission to BMC Infectious Diseases - INFD-D-19-01788R2

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Date: Sunday, 17 November 2019, 02:30 pm GMT+7

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INFD-D-19-01788R2

First-line antibiotics susceptibility pattern of toxigenic *Corynebacterium diphtheriae* in Indonesia  
Dominicus Husada, MD, PhD; Sugi Deny Pranoto, MD, Pediatrician; Indra Suwarin Kurniawati, Bachelor; Adi Pramono  
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## Decision on your Submission to BMC Infectious Diseases - INFD-D-19-01788R3

From: BMC Infectious Diseases Editorial Office (em@editorialmanager.com)

To: dominicushusada@yahoo.com

Date: Wednesday, 27 November 2019, 06:17 pm GMT+7

INFD-D-19-01788R3

First-line antibiotics susceptibility pattern of toxigenic *Corynebacterium diphtheriae* in Indonesia  
Dominicus Husada, MD, PhD; Sugi Deny Pranoto, MD, Pediatrician; Indra Suwarin Kurniawati, Bachelor; Adi Pramono Hendrata, MD; Eveline Irawan, MD; Leny Kartina, MD, Pediatrician; Dwiyanti Puspitasari, MD, Pediatrician; Parwati Setiono Basuki, Profesor, MD, Pediatrician; Ismoedijanto Moedjito, Profesor, MD, Pediatrician  
BMC Infectious Diseases

Dear Mr Husada,

I am pleased to inform you that your manuscript ""First-line antibiotics susceptibility pattern of toxigenic *Corynebacterium diphtheriae* in Indonesia"" (INFD-D-19-01788R3) has been accepted for publication in BMC Infectious Diseases.

If any final comments have been submitted from our reviewers or editors, these can be found at the foot of this email for your consideration.

Before publication, our production team will also check the format of your manuscript to ensure that it conforms to the standards of the journal. They will be in touch shortly to request any necessary changes, or to confirm that none are needed.

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Please do not hesitate to contact us if you have any questions regarding your manuscript and I hope that you will consider BMC Infectious Diseases again in the future.

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