PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Carrier prevalence and risk factors for colonization of multiresistant bacteria in Danish emergency departments - A cross-sectional survey
AUTHORS	Skjøt-Arkil, Helene; Mogensen, Christian; Lassen, Annmarie; Johansen, Isik; Chen, Ming; Petersen, Poul; Andersen, Karen; Ellermann-Eriksen, Svend; Møller, Jørn; Ludwig, Marc; Fuglsang-Damgaard, David; Nielsen, Finn; Petersen, Dan; Jensen, Ulrich; Rosenvinge, Flemming

VERSION 1 – REVIEW

REVIEWER	Barnaby Young National Centre for Infectious Diseases
REVIEW RETURNED	11-Feb-2019

GENERAL COMMENTS	This is a well designed and conducted study. Major comments: 1. Interpretation of the results is limited by the authors presenting only a univariate analysis. I agree it is not possible to conduct a multivariable analysis for MRSA/VRE/CPE with the low numbers - but it would be beneficial to conduct this for ESBL. 2. In addition, further microbiological detail would be useful: perhaps focusing on ESBLs given there numbers, for example, resistance to other antibiotics (e.g. quinolones, aminoglycosides), which organisms were cultured, and any genetic information (plasmids/beta-lacatamses). If space allows, and while this is available in the published study protocol, an overview of the microbiological methods would be useful. Some other minor points: 1. What happened to the c.diff results? 2. Table 4 contains many variables which makes reading difficult - many of the subgroups can be collapsed. 3. A more detailed consideration of how these study results might affect screening programmes used by emergency departments in Denmark is needed to make sense of why this study is important (even if some of this will be addressed in a separate paper).

REVIEWER	Shmuel Benenson Hadassah-Hebrew University Medical Center, Israel
REVIEW RETURNED	25-Feb-2019

GENERAL COMMENTS	The study describes MDR bacteria carrier prevalence among adults visiting the ED in 8 Danish ED's. The authors found 5.2% MDR carriage rate among these patients; most were ESBLs (4.5%), and the prevalence of CPE, VRE and MRSA was very low (0.1-0.4%). The authors also analysed the association between MDR carriage and potential risk factors. They found that previous antibiotic use and treatment at foreign hospital were risk factors for MDR carriage (Odds ratio 1.6 and 5.1 respectively). This is a well designed multi-center study in one country with an enviable very low prevalence of MDR bacteria. As the authors state in the limitations, the external validity of the study is restricted to countries with a low MDR prevalence. Additionally, since the MDR prevalence is so low, the power to find risk factors is also very low. One can not perform multiple comparisons in such a small cohort of positive carriers as was done in this study. It leads to a very wide confidence intervals as presented in Table 4. Moreover, the epidemiological literature is saturated with studies looking for risk factors for MDR carrier state and thus the findings in this part of the study are not innovative. I think that the findings of the study, mainly the MDR carrier rates, may be of interest to the scientific community but I suggest to sorten it to a "Letter to the Editor". Minor comments: 1. Methods, eligibility criteria: "mentally competent" - this rule precludes patients with dementia who usually stay in long term care facilities where the MDR prevalence rate is usually higher. 2. Collection of swabs - did the patients were asked to perform the swabbing or it was done by the ED staff? The sensitivity of self swabbing is lower. 3. Results, page 6 last paragraph: the sentence which begins with "Of the eight..." is not clear. 4. The use of univariate logistic regression for the analysis is puzzling. The authors should explain why this method was chosen. 5. The discussion is too long and should be shortened. 6. Table 2 is unnecessary. These are not results and should be shortly summarized in the text.

VERSION 1 – AUTHOR RESPONSE

Reply to reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Barnaby Young
Institution and Country: National Centre for Infectious Diseases
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
This is a well designed and conducted study.

Major comments:

1. Interpretation of the results is limited by the authors presenting only a univariate analysis. I agree it is not possible to conduct a multivariable analysis for MRSA/VRE/CPE with the low numbers - but it would be beneficial to conduct this for ESBL.
ANSWER: As suggested we have conducted a multivariate analysis for ESBL.

2. In addition, further microbiological detail would be useful: perhaps focusing on ESBLs given there numbers, for example, resistance to other antibiotics (e.g. quinolones, aminoglycosides), which organisms were cultured, and any genetic information (plasmids/beta-lacatamses).
ANSWER: We have added a table indicating the numbers of in-vitro susceptible isolates

			Number of in-vitro susceptible isolates (%)[*2]				
	Species	Number of	Meropenem	Piperacillin-tazobactam	Gentamicin	Ciprofloxacin	Beta-lactamase
ESBL n=247	*E. coli*	203	203 (100)	175 (86)	153 (75)	97 (48)	na
	Klebsiella pneumoniae	35	34 (97)	17 (49)	26 (74)	6 (17)	na[*4]
	Klebsiella oxytoca	6	6 (100)	4 (67)	2 (33)	1 (17)	na
	Other[*3]	2	2 (100)	1	1	1	na
CPE n=6	*E.coli*	3	0	0	1 (33)	0	OXA-48 (2),
	Other[*6]	3	0	0	2 (67)	0	NDM (3)

ESBL: Extended-spectrum beta-lactamase producing enterobacteria
CPE: Carbapenemase producing enterobacteria
[*1] Eleven patients were colonized with more than one ESBL producing enterobacteria and two patients were colonized with two different CPE (different species or susceptibility pattern).
[*2] According to EUCAST breakpoints (www.eucast.org).
[*3] One *Klebsiella spp*, and one *Citrobacter koseri.*
[*4] One isolate of *Klebsiella pneumoniae* was both ESBL and NDM positive.
[*5] One isolate was both OXA-48 and NDM positive.
[*6] One *Enterobacter cloacae*, one *Klebsiella pneumoniae* and one *Citrobacter freundii*.

If space allows, and while this is available in the published study protocol, an overview of the microbiological methods would be useful.
ANSWER: We have added the following to the Microbiological analysis section: "*Briefly outlined, samples were screened with commercially available, selective, chomogenic agar media [(MRSA: CHROMagar MRSA II agar, ESBL: CHROMagar ESBL bi-agar (Becton Dickinson, Heidelberg, Germany)), (CPE: chromID CARBA SMART agar, VRE: chromID VRE agar (bioMérieux, Marcy-l'Etoile, France))]. A preceding enhancement broth step was used for both VRE and MRSA. All isolates were identified by mass spectrometry (MALDI-TOF) and the presence of resistance genes in MRSA (mecA/mecC) VRE (vanA/vanB) and CPE (bla_{KPC}/bla_{NDM}/bla_{VIM}/bla_{OXA-48}/bla_{IMP}) was confirmed by polymerase chain reaction. ESBL-production was confirmed phenotypically (synergism between clavulanic acid and cefotaxime, ceftazidime and/or cefepime).* "

Some other minor points:

1. What happened to the c.diff results?
ANSWER: The C.diff results wil be presented in an independent manuscript

2. Table 4 contains many variables which makes reading difficult - many of the subgroups can be collapsed.

ANSWER: Thank you for the suggestion. We have collapsed the subgroups which we hope make the reading improved. The larger observations in the collapsed subgroup have made it possible to perform a multivariate analysis for all colonized bacteria (see table 5).

3. A more detailed consideration of how these study results might affect screening programmes used by emergency departments in Denmark is needed to make sense of why this study is important (even if some of this will be addressed in a separate paper).
ANSWER: Thank you for the comment. We have added the sentence "*This might affect the questions in the patient interview or which bacteria to identify in the current screening programs*" to the discussion section. As reviewer 2 suggests shortening the discussion section, we have not discussed it further.

Reviewer: 2
Reviewer Name: Shmuel Benenson
Institution and Country: Hadassah-Hebrew University Medical Center, Israel
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
The study describes MDR bacteria carrier prevalence among adults visiting the ED in 8 Danish ED's. The authors found 5.2% MDR carriage rate among these patients; most were ESBLs (4.5%), and the prevalence of CPE, VRE and MRSA was very low (0.1-0.4%). The authors also analysed the association between MDR carriage and potential risk factors. They found that previous antibiotic use and treatment at foreign hospital were risk factors for MDR carriage (Odds ratio 1.6 and 5.1 respectively).

This is a well designed multi-center study in one country with an enviable very low prevalence of MDR bacteria. As the authors state in the limitations, the external validity of the study is restricted to countries with a low MDR prevalence. Additionally, since the MDR prevalence is so low, the power to find risk factors is also very low. One can not perform multiple comparisons in such a small cohort of positive carriers as was done in this study. It leads to a very wide confidence intervals as presented in Table 4. Moreover, the epidemiological literature is saturated with studies looking for risk factors for MDR carrier state and thus the findings in this part of the study are not innovative.
I think that the findings of the study, mainly the MDR carrier rates, may be of interest to the scientific community but I suggest to sorten it to a "Letter to the Editor".
ANSWER: We find our results are of interest in countries with similar MRB carrier prevalences, where this study is the only multicenter study. We find that the format of a "letter to the editor" would be a too short format for the interested readers

Minor comments:
1. Methods, eligibility criteria: "mentally competent" - this rule precludes patients with dementia who usually stay in long term care facilities where the MDR prevalence rate is usually higher.
ANSWER: Thank you for the comments. Unfortunately we had to exclude patients with dementia. We have added this to the limitation part of the discussion section.

2. Collection of swabs - did the patients were asked to perform the swabbing or it was done by the ED staff? The sensitivity of self swabbing is lower.
ANSWER: Thank you for the question. The swabbing was performed by the project staff. This information has been added to the method section.

3. Results, page 6 last paragraph: the sentence which begins with "Of the eight..." is not clear.
ANSWER: We have improved the sentence to. "Of the 266 MRB-positive patients, eight (3%) patients were re-attendances"

4. The use of univariate logistic regression for the analysis is puzzling. The authors should explain why this method was chosen.
ANSWER: We have collapsed the subgroups in the analysis as suggested by reviewer 1, which have made it possible to perform a multivariate analysis for all colonized bacteria (see table 5).

5. The discussion is too long and should be shortened.
ANSWER: We agree that the discussion section is long. We have tried to shorten it as suggested.

6. Table 2 is unnecessary. These are not results and should be shortly summarized in the text.
ANSWER: 'Table 2 Comparative profile of declined and analysed cohort' has been deleted and summarized in the text as suggested.

VERSION 2 – REVIEW

REVIEWER	Barnaby Young Tan Tock Seng Hospital
REVIEW RETURNED	24-Apr-2019

GENERAL COMMENTS	The revisions combining some of the subgroups and performing a multivariable analysis have made the study findings much easier to understand. I am not sure the multivariable analysis in Table 5 really adds anything - >85% of isolated MRB were ESBL, so the results are very similar to the analysis in Table 4. The risk factors for colonisation with the different bacteria will also vary (particularly for MRSA versus VRE/CRE/ESBL). I would suggest removing this and just comparing the ESBL multivariable analysis with the univariate analysis for the other 3 MRBs as presented in Table 4. - Typo in Table 2 where in the MRSA heading is listed as n=15, where I think it should be 16

VERSION 2 – AUTHOR RESPONSE

Thank you very much for your response on our paper "Carrier prevalence and risk factors for colonization of multiresistant bacteria in Danish emergency departments - A cross-sectional survey". We are happy, that the reviewer found our revised manuscript improved. We have made the changes as suggested by the reviewer. Changes to the manuscript have been marked using track changes function in word. We hope that our revisions have improved out manuscript sufficiently to be acceptable for publication in your journal.

If you have any questions, please do not hesitate to contact me.