Author's response to reviews

Title: Burden of carbapenem-resistant organisms in the Frankfurt/Main Metropolitan Area in Germany 2012/2013 - first results and experiences after the introduction of legally mandated reporting

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Author's response to reviews:

Dear Cherry,

I have just tried to attach two additional files with individual responses to each of the two reviewers, which however did not work. Therefore I will just paste the text files of the individual responses right after this text which was intended as a general text for both reviewers.

Many thanks for the numerous very helpful comments from both referees. We believe that the manuscript has greatly improved by incorporating the referee’s suggestions. Particular thanks to a comment from referee 2 on an unlikely pairing of a species and a carbapenemase in our original document. We have taken this information as reason to re-evaluate our complete data set and have found some faults in the database which we could fortunately correct. The data were double checked, every 5th data record was re-entered starting from the original reporting form. Some details in the figures presented in the text had to be adapted. Yet, the main findings remained unchanged. On advice of referee 1 a separate paragraph discussing the limitations of the study has been added which certainly helps to walk the reader through the limitations encountered with a study of this type in a succinct and structured way. On advice of both referees the conclusions could be formulated in a more precise way. And finally, the many and in case of referee 2 the extremely detailed comments, have very much helped to improve also minor aspects of the document.

I have added comments to the changes suggested by each referee in two separate documents which go through each referee’s suggestions point by point.

We had intensive discussions related to the figure 1 in the document displaying the notified CROs by species and month. We suggest to keep the original layout, which we have slightly modified to improve readability. However, we have also generated an alternative display form in which each species is presented in a
separate graph and which could be displayed as a multi-panel figure.

Again many thanks to the referees and best regards,

Niels Kleinkauf

Comments to the changes suggested by referee 1

Major Compulsory Revisions

- The article is well written but would profit from shortening of the text and tables/figures in order to make it more concise (especially methods section and discussion).

Several passages of the manuscript have been revised, also on request of reviewer 2. In total the manuscript could be shortened. Figure 2 has been deleted. The information enclosed in the figure has been added to the text, section “Results”, lines 148-154.

- The reference list should also be considerably shortened and should only include articles that are related to the findings of this article. Most references relate to NDM, even though only 4 NDM positive isolates were reported in this study and NDM is by far not the dominating carbapenemase in Germany. The number of references in German language should also be minimized as they are not universally understood by most readers of the journal; some references do not contain any relevant data on CRO (e.g. ref. 26, 27) and could be omitted without compromising the content of the article.

The reference list has been shortened considerably. Of the originally 27 references, 5 have been deleted.

Minor Essential Revisions

- The figure 1 is difficult to read; it could be improved by choosing a different
format (e.g. bar or line diagram with the month of the study on the x-axis) and colors which can be more easily distinguished.

Figure 1 has been modified to improve readability and better show the month on the x-axis. As possible alternative we have generated an alternative presentation form in which each species is presented in a separate bar graph which could be displayed in a multi-panel figure. In our opinion, however, the improved original format is better suited to show the different relative proportions of each species.

- There are remarkable differences in the incidence of CROs between the different hospitals (fig. 2) – how can they be explained?

Unfortunately the data that can be collected by a passive surveillance system based on notifications mandated by state law do not allow to request every available information that may be of interest. Furthermore, the information provided is subject to a certain level of data protection. This does not allow us to add information that allows a simple and definite identification of facilities reported on.

Concerning the data reported in the manuscript, the hospital with the most reported cases and the highest incidence is the university hospital of Frankfurt/Main. However the information needs to be anonymized in a publication of this type. An indication of the properties of this clinic has been added in the “Discussion” section, lines 215-219

- How does the reported incidence of 0.127 notifications/1000 patient days compare to that of other studies?

This is an issue for which it would be nice to have an answer to. However since currently CROs are not reportable at national level, there is a lack of comparable data. A call for a countrywide reporting has been added in the “Conclusion” section, lines 336-338.

- Please discuss the limitations of the study (most likely underreporting in the beginning of the study time, as could be suggested by the numbers of P. aeruginosa in fig. 1).
A section discussing the limitations of the study has been added to the manuscript. See section “Discussion”, lines 297-313.

- Please correct the spelling of A. baumannii throughout the document.

The spelling has been corrected throughout the document.

- In the conclusion section, the authors write that Frankfurt is in a critical phase – how is that backed up by the data provided? You might want to rephrase this sentence in order to be clearer.

This section has been rephrased. Please see lines 326-338

Discretionary Revisions

The suggested revisions have been included in the text.

Comments to the changes suggested by referee 2:

A) Since the mandatory reporting was introduced in the whole German federal state (Hesse) it would be interesting to have some common facts: Please give the number of inhabitants and hospitals in Hesse and the whole number of noticed CROs in the 12-months period.

The information has been added in the section “Methods”, lines 101-112.
Keywords: Please use only keywords that were not mentioned in the manuscript title and avoid unnecessary abbreviations.

The keywords have been changed.

Table 1: It is not a table – delete it and include the information in the part “Methods”.

The table 1 contains a lot of information relevant for the understanding of the text in a compact format. We would like to keep it in order not to unnecessarily lengthen the manuscript and to allow a rapid overview of the diverse data currently contained in the table.

Table 2: It is very uncommon that a K. pneumoniae produces OXA-23 and an A. baumannii produces OXA-48 – Please check these results again and repeat the analyses (species and carbapenemase confirmation).

Many thanks for this extremely helpful comment. We have taken this information as reason to re-evaluate our complete data set and have found some faults in the database which we could fortunately correct. The data were double checked, every 5th data record was re-entered starting from the original reporting form. Several details in the text had to be adapted. Yet the main findings remained unchanged.

Figures 1 and 2 are not necessary – the information can be included in brief in the manuscript text – Please delete these figures.

- We would like to keep Figure 1. We believe that the graphical presentation of the data is the best way to present the information included. The figure has been adapted to better show the month on the x-axis. The different relative proportions of each species as well as the variation over time are shown in an easily comprehensible format.

As possible alternative we have generated an alternative presentation form in
which each species is presented in a separate bar graph which could be displayed in multi-panel figure. In our opinion, however, the improved original format is better suited to show the different relative proportions of each species.

- Figure 2 was deleted. The information has been included in the manuscript text, section “Results”, lines 148-154.

Methods: Please include the criteria for mandatory reporting in according reference 15 and table 1.

The criteria for reporting are relatively complex. This is why we would like to keep the information as a table. In our understanding the inclusion in the text of the methods section offers no advantage. Particularly since readers may be inclined to refer to this information while reading different sections of the text a table seems to us to be the most appropriate form of presentation.

Methods: Please describe how carbapenemase confirmation was performed in the laboratories – Which phenotypic tests and which genotypic test systems were used?

The request of information on laboratory methodology is not part of mandated reporting. For a few laboratories with whom the public health authority has good contacts detailed information is available. Yet unfortunately we cannot request every laboratory to provide information which is not part of the mandated reporting.

One risk for emergence and selection of CROs is the usage of carbapenems– were information collected on the previous treatment of the patients?

No, though we agree that this would be interesting information, the decision on which information to collect within the context of mandated reporting in Hesse lies with the ministry of social affairs. This information has not been included in the data to be reported.
Discussion: This part is very long and contains a lot of repetition of results – comments see below.

Further comments:

Line 43-45: Include one or two sentences with reporting criteria (include the information “Frankfurt residents” from line 49 in this sentence).

The detailed reporting criteria are relatively complex and are better presented in Table 1

Line 61: Imipenem was introduced in 1985 – more than 25 years ago. Please rephrase.

The sentence was rephrased. The intention is to mention that carbapenems are a class of antibiotics which were hardly affected by resistance issues for a comparatively long time period, namely an approximate 20 years, after which resistance has started to become a substantial clinical problem.

Line 64-67: The meaning of these sentences is not clear – please rephrase this part and avoid the word “reserve antibiotics”.

The passage was rephrased. The term “reserve antibiotics” was replaced by the term “second-line antibiotics”.

Line 87: Quit the sentence after “2012” and include further information from line 88-91 in the part “Methods”.

The sentence was rephrased. See also comment F.

The text has been deleted. The term is a direct translation of the title of the decree issued by the ministry of social affairs and refers to resistance through transmissible or mobile genetic elements such as plasmids which have been "acquired" by a bacterial strain as opposed to being inherent resistance traits usually located on the bacterial chromosome.

Line 128: Explain what is meant with "not fulfilling criteria" and give the number of patients after the number of isolates.

The text has been deleted. The explanation was given in parentheses, i.e. notifications received by the public health authority but relating to species not reportable such as S. maltophilia, or isolates with a non-reportable susceptibility profile were deleted from the data set.

Line 134: Give in brief in which (most prevalent) species a carbapenemase was detected and give the three most prevalent carbapenemase types that were detected. Include information how the carbapenemase detection was performed.

The information is included in table 2.

Line 136-138: Here more information would be helpful – which species were involved (carbapenemase producers? infection or colonisation?) and what is knows about the patients (travel history?, nationality?, hospitalisation abroad?, in countries with high prevalence for CROs? Previous antibiotic treatment?)

The text was deleted in order to shorten the text since the information was considered to be of minor relevance to the manuscript.

Line 140: What is known on these outpatients regarding previous hospitalisation? Give information on infection/colonisation, travel background etc. (maybe include it in the discussion part).
The information was added to the text. See section “Results”, lines 158-162.

Line 143-152: Characterise (maybe in the discussion part) the hospital with the most reported cases and the hospital with the highest incidence/100patient days – are they identical? What are the properties of these clinic(s) in comparison to the others (number of beds/patients, special patients/wards, screening procedures etc.? Explain what is meant with “case mix and unit-based”.

Yes the hospital with the most reported cases and the highest incidence are identical. It is the university hospital of Frankfurt/Main. However the information provided within the context of mandatory notification does not allow us to name individual reporting facilities. The information needs to be anonymized in a publication of this type. An indication of the properties of this clinic has been added in the “Discussion” section, lines 215-219.

The term “case mix” indicates the average mix of a healthcare facilities (or units= type of patient. For example a surgical ward in a hospital may have a large proportion of young and otherwise healthy accident victims while another surgical ward will have a large proportion of older and immunocompromised tumour patients which are far more susceptible to bacterial infections.

The term “unit-based” refers to the different units/wards within a hospital. For example an intensive care unit within different hospitals may provide treatment for very different patient groups.

Line 157-159: Include the three main foreign countries/regions that were identified.

The information is contained in the Table 2. No text was added. From our point of view the interested reader can readily retrieve the information from the table.

Line 161: Explain which kind of infections – if the following sentence includes this information.
No detailed information on the type of infection is provided within the context of mandatory reporting.

Line 165: Explain “history of inpatient treatment”.

The text has been rephrased. The term “history of inpatient treatment” has been replaced by “history of previous hospitalization” See section “Results”, lines 172-173.

Line 165-168: Is there a correlation between sampling site and occurrence of infection – which CRO species causes the most infections?

No information was provided concerning the type and severity of infection. A meaningful correlation can therefore not be calculated.

Line 169: Was a routine screening (of patients at risk?) introduced in the hospitals or were the finding of CROs in the first two days due to occurrence of signs of infection with admittance to the hospital?

The data presented in the manuscript are results of a passive surveillance system based on reporting mandated by state law. In contrast to a clinical study only limited data can be requested from the reporting parties.

No information on the type and frequency or the criteria of screening programs was collected.

Independent of the reason for sampling, detection of CROs in the first days of hospitalization may be an indication of transmission in the community setting.

Line 174-186: Long and the repetition of the categories is not necessary – give only the main facts for Germany: occurrence of sporadic cases and outbreaks (give references) and suspected regional spread of carbapenemases (which types? – give references).
The text has been rephrased. The detailed listing of the categories was omitted. See section “Discussion”, lines 184-191.

Line 193-194: Include information that the patient was from Serbia according references.

The information was added. See section “Discussion”, line 199.

Line 197-203: Repetition of results – discuss it: Is anything known about the screening frequency in the 17 hospitals, esp. the ones with the highest incidence of CROs. Here can be given other properties of these hospitals (size, beds, number of patients, special patients/wards etc.)

See comments to your remarks “line 143-152” and “line 169”.

Line 204-208: Repetition of results – discuss it: What is known on these outpatients? Give information on infection/colonisation, travel background etc.

Information has been added. See section “Discussion”, lines 223-224.

Line 208-211: Repetition of results – discuss it: What is known on this single hospital (give characteristics)?

See comment to your remark “line 143-152”.

Line 214-217: Repetition of results – make it short!

The sentence was rephrased.

Line 220-222: Give examples (countries with high prevalence) and references.
The information is given in Table 2.

Line 224-225: How many of these patients were hospitalised/came from abroad?

The number of patients with place of residence and prior hospitalization abroad is given in Table 2.

Line 228-231: What is meant with “several” – please give the number. “could” the patients be isolates or “were” they isolated? Please explain.

The sentence was rephrased. The term “could” was replaced by “were”. An exact number is difficult to give, since we know only in some cases for sure that the carrier status was known. Exact analysable statistics have not been performed. As written in section “Discussion”, line 270-272 healthcare facilities in Hesse are obliged to inform about CRO findings when transferring patients.

Line 235: Give the CRO (carbapenemase type) for the two cases/patients.

The information was added to the manuscript. See section “Discussion”, lines 250-251.

Line 238-244: The paragraph is not clear - What does it mean? Should the CDC prevention strategies be introduced or not – rephrase and discuss.

The measures that could be implemented are discussed in section “Discussion”, lines 269-278.

Line 245-264: Combine the two paragraphs – name implemented measurements
and the problems in detail, e.g. the problem of late reporting (carbapenemase confirmation) and the consequences.

See comment above

Line 270: Give details – species and carbapenemase type (if detected).

The information was added to the manuscript. See section “Discussion”, lines 285-287.

Line 285-289: Explain how these “major efforts are being made” (information events, training programs, controls etc?).

The paragraph was rephrased. Explanations were added in section “Discussion”, lines 315-321.

Line 290: What is meant with medical tourism – patients that came from abroad only for surgical interventions? How big is the problem in Frankfurt/main region – how much patients in the present study were “medical tourists”? Were German patients with previous hospitalisation abroad also included in this definition?

The paragraph has been rephrased. The term “medical tourism” has been replaced with the term “cross-border transfer of patients”. The exact extent of the problem cannot be quantified due to lack of detailed information.

Line 297: This is a result – make a conclusion. It indicates a possible community spread of CROs (if travel abroad, previous hospitalisation etc. can be excluded in these six cases?). Please rephrase.

The sentence has been rephrased.
Line 300-302: The call for a country-wide reporting should be included in the conclusion.

The text was included in the conclusion. See section “Conclusion”, lines 336-338.

Minor comments:

The suggested modifications of the manuscript have been added.