First patient-to-patient intra-hospital transmission of a Clade I C. auris in France revealed after a two-months incubation period

Alexandre Alanio, Hannah Snell, Camille Cordier, Marie Desnos-Ollivier, Sarah Dellière, Samia Hamane, Aude Sturny-Leclère, Elodie Da Silva, Nesrine Aissaoui, Cyril Eblé, Martine Rouveau, Micheline Thégat, Widad Zebiche, Matthieu Lafaurie, Blandine Denis, Sophie Touratier, Mourad Benyamina, Emmanuel Dudoignon, Christina Cuomo, and Francois Dépret

Corresponding Author(s): Alexandre Alanio, Institut Pasteur

Review Timeline:
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- Editorial Decision: July 19, 2022
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- Editorial Decision: August 18, 2022
- Revision Received: August 25, 2022
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Editor: Damian Krysan
Reviewer(s): The reviewers have opted to remain anonymous.

Transaction Report:
(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. The original formatting of letters and referee reports may not be reflected in this compilation.)

DOI: https://doi.org/10.1128/spectrum.01833-22
Re: Spectrum01833-22 (First patient-to-patient intra-hospital transmission of a Clade I C. auris in France revealed after a two-months incubation period)

Dear Prof. Alexandre Alanio:

I have reviewed your manuscript entitled "First patient-to-patient intra-hospital transmission of a Clade I C. auris in France revealed after a two-months incubation period", and I regret to inform you that we will not be able to publish it in Spectrum. Specifically, I have decided that the manuscript is outside of the scope for a microbiology journal such as Microbiology Spectrum and more appropriate for hospital epidemiology- or infection control-control focused journal. The findings are much more in line with these venues than with Spectrum.

I am sorry to convey a negative decision on this occasion, but I hope that the enclosed reviews are useful. Please note, rejections from Microbiology Spectrum are final and your manuscript will not be considered by other ASM journals. We wish you well in publishing this report in another journal and hope that you will consider Spectrum in the future.

The ASM Journals program strives for constant improvement in our submission and publication process. Please tell us how we can improve your experience by taking this quick Author Survey.

Sincerely,

Damian Krysan
Editor, Microbiology Spectrum

Reviewer comments:
August 18, 2022

Prof. Alexandre Alanio
Institut Pasteur
Molecular Mycology Unit
28, rue du Dr Roux
Bat Duclaux aile Fournau RDC Haut
Paris 75724
France

Re: Spectrum01833-22R1-A (First patient-to-patient intra-hospital transmission of a Clade I C. auris in France revealed after a two-months incubation period)

Dear Prof. Alexandre Alanio:

As you will read from the reviewers comments, there was some disagreement on the need for additional revisions. Reviewer 1 raises some important points regarding the strength of the conclusion that person-to-person transmission is the most likely mechanism. I think it would be best to soften this conclusion and provide a balanced commentary on alternate mechanisms in the revision. You may also want to soften a call for additional testing by suggesting that these approaches might provide reasonable approaches that could be studied in the future. The latter was also raised by reviewer 2. Careful attention to these comments as well as the other more minor issues is in order.

Thank you for submitting your manuscript to Microbiology Spectrum. When submitting the revised version of your paper, please provide (1) point-by-point responses to the issues raised by the reviewers as file type "Response to Reviewers," not in your cover letter, and (2) a PDF file that indicates the changes from the original submission (by highlighting or underlining the changes) as file type "Marked Up Manuscript - For Review Only". Please use this link to submit your revised manuscript - we strongly recommend that you submit your paper within the next 60 days or reach out to me. Detailed instructions on submitting your revised paper are below.

Link Not Available

Below you will find instructions from the Microbiology Spectrum editorial office and comments generated during the review.

ASM policy requires that data be available to the public upon online posting of the article, so please verify all links to sequence records, if present, and make sure that each number retrieves the full record of the data. If a new accession number is not linked or a link is broken, provide production staff with the correct URL for the record. If the accession numbers for new data are not publicly accessible before the expected online posting of the article, publication of your article may be delayed; please contact the ASM production staff immediately with the expected release date.

The ASM Journals program strives for constant improvement in our submission and publication process. Please tell us how we can improve your experience by taking this quick Author Survey.

Sincerely,

Damian Krysan
Editor, Microbiology Spectrum

Journals Department
American Society for Microbiology
1752 N St., NW
Washington, DC 20036
E-mail: spectrum@asmusa.org

Reviewer comments:

Reviewer #1 (Comments for the Author):
The manuscript "First patient-to-patient intra-hospital transmission of a Clade I C. auris in France revealed after a two-months incubation period" by Alanio, et al., describes the first two patients with C.auris in a burn ICU. One of these patients had a positive blood culture and the other was colonized. The manuscript focuses on the kinetics of colonization of the second patient and argues that "person to person transmission" occurred but that the second patient had a prolonged incubation period prior to detection of colonization.

The authors present data that the second patient (P1) had a series of negative qPCR screening tests prior to becoming colonized. They report "It took more than 41 days for C. auris to significantly colonize the body of P1 and be finally detectable on all sites despite three negative weekly screening tests."

The limited number of SNPs between the two strains strongly supports the conclusion that the patients both had highly related strains that almost certainly had a common source. The first patient (P0) was mostly likely colonized on admission; this is the most likely source of the isolate.

The fact that the patients' isolates are related does not mean that there was "patient-to-patient" transmission of the organism. The authors cite many references and present their own data that C.auris persists on environmental surfaces for weeks to months. It can also be found on the hands of healthcare workers. The authors do not describe any direct contact between P0 and P1. It is far more likely that P1 acquired C.auris via nosocomial horizontal transmission related to environmental contamination with C.auris. This is by far the most frequently described mechanism of hospital-acquired C.auris and the simplest explanation for this transmission event. This mechanism of transmission is central to the manuscript because the authors conclude that P1 was colonized/infected with C.auris 41-61 days prior to P1's positive tests because that is the window of time when both P0 and P1 were hospitalized. There is no data to support a prolonged "incubation period" in P1. More likely, the environment was contaminated with C.auris from P0 and this contamination persisted long after P0 was discharged. P1 could have acquired colonization with C.auris from the environment at any time prior to P1's positive tests.

Other concerns include:
1. The manuscript still contains many phrases that are difficult to follow.
2. The authors refer to their institutional policies on C.auris surveillance in the text. These policies should be provided as supplemental material.
3. References 13-16 are various agency guidelines about C.auris infection prevention. Links to these guidelines or more specific information about where the reader can access the guidelines should be included. Reference 15 doesn't provide any source for the guideline.
4. The authors recommend that patients be screened at more sites than in their institutional guidelines and with culture techniques in addition to qPCR techniques without providing evidence to support this conclusion.

Reviewer #2 (Comments for the Author):

The authors have addressed the comments of prior review. The manuscript is easy to follow and interesting. I have the few suggestions for clarifications that would be helpful for the reader.

Were patients P0 and P1 negative for C. auris prior to the study, or untested?

Were other patients routinely screened on the floor/unit/building?

The authors suggest guideline changes may be needed. What guideline changes would they suggest and what type of cost may be associated?

Staff Comments:

Preparing Revision Guidelines

To submit your modified manuscript, log onto the eJP submission site at https://spectrum.msubmit.net/cgi-bin/main.plex. Go to Author Tasks and click the appropriate manuscript title to begin the revision process. The information that you entered when you first submitted the paper will be displayed. Please update the information as necessary. Here are a few examples of required updates that authors must address:

• Point-by-point responses to the issues raised by the reviewers in a file named “Response to Reviewers," NOT IN YOUR COVER LETTER.
• Upload a compare copy of the manuscript (without figures) as a "Marked-Up Manuscript" file.
• Each figure must be uploaded as a separate file, and any multipanel figures must be assembled into one file.
• Manuscript: A .DOC version of the revised manuscript
• Figures: Editable, high-resolution, individual figure files are required at revision, TIFF or EPS files are preferred
For complete guidelines on revision requirements, please see the journal Submission and Review Process requirements at https://journals.asm.org/journal/Spectrum/submission-review-process. **Submissions of a paper that does not conform to Microbiology Spectrum guidelines will delay acceptance of your manuscript.**

Please return the manuscript within 60 days; if you cannot complete the modification within this time period, please contact me. If you do not wish to modify the manuscript and prefer to submit it to another journal, please notify me of your decision immediately so that the manuscript may be formally withdrawn from consideration by Microbiology Spectrum.

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Corresponding authors may [join or renew ASM membership](https://www.asmusa.org/membership/join) to obtain discounts on publication fees. Need to upgrade your membership level? Please contact Customer Service at Service@asmusa.org.

Thank you for submitting your paper to Microbiology Spectrum.
As you will read from the reviewers comments, there was some disagreement on the need for additional revisions. Reviewer 1 raises some important points regarding the strength of the conclusion that person-to-person transmission is the most likely mechanism. I think it would be best to soften this conclusion and provide a balanced commentary on alternate mechanisms in the revision. You may also want to soften a call for additional testing by suggesting that these approaches might provide reasonable approaches that could be studied in the future. The latter was also raised by reviewer 2. Careful attention to these comments as well as the other more minor issues is in order.

Reply: Thank you for time and your comments. We responded to all reviewer’s comments and modified the manuscript accordingly. This improved clearly the discussion. We hope that our manuscript will be accepted based on our revised version.

Sincerely,

Pr Alexandre Alanio

Reviewer #1 (Comments for the Author):

The manuscript "First patient-to-patient intra-hospital transmission of a Clade I C. auris in France revealed after a two-months incubation period" by Alanio, et al., describes the first two patients with C.auris in a burn ICU. One of these patients had a positive blood culture and the other was colonized. The manuscript focuses on the kinetics of colonization of the second patient and argues that "person to person transmission" occurred but that the second patient had a prolonged incubation period prior to detection of colonization.

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The limited number of SNPs between the two strains strongly supports the conclusion that the patients both had highly related strains that almost certainly had a common source. The first patient (P0) was mostly likely colonized on admission; this is the most likely source of the isolate.

The fact that the patients' isolates are related does not mean that there was "patient-to-patient" transmission of the organism. The authors cite many references and present their own data that C.auris persists on environmental surfaces for weeks to months. It can also be found on the hands of healthcare workers. The authors do not describe any direct contact between P0 and P1.

It is far more likely that P1 acquired C.auris via nosocomial horizontal transmission related to environmental contamination with C.auris. This is by far the most frequently described mechanism of hospital-acquired C.auris and the simplest explanation for this transmission event.

This mechanism of transmission is central to the manuscript because the authors conclude that P1 was colonized/infected with C.auris 41-61 days prior to P1's positive tests because that is the window of time when both P0 and P1 were hospitalized. There is no data to support a prolonged "incubation period" in P1. More likely, the environment was contaminated with C.auris from P0
and this contamination persisted long after P0 was discharged. P1 could have acquired colonization with C. auris from the environment at any time prior to P1's positive tests.

Reply: We agree with reviewer that contamination from the environment is a very likely hypothesis. We were not clear enough in our manuscript. Action: We modified the first chapter of the discussion to make Reviewer's hypothesis clearly stated and discussed line 149-171: “We describe here the kinetics of colonization to C. auris of one patient in a burn ICU who acquired Clade I strain from another patient who was admitted most probably with C. auris colonization. It took more than 41 days for C. auris to detect colonization of P1 and to be finally detectable on all sites despite three negative weekly screening tests. It is clear from the genetic analysis revealing a low number of SNPs between P0 and P1 strains (n<12), as already described in outbreak investigations (17), that the P0 strain have been transmitted to P1. Beyond this analysis, two likely scenarios coexist: (i) the contamination of P1 could have occur at very early steps after admission, at the time where P0 was not known to be C. auris-positive (Figure 1) either by a contaminated shared material or by healthcare worker hands, since no contact between patients was possible in ICU; (ii) Some C. auris persisted in the environment allowing P1 contamination either early or later on, leading to C. auris detection after a period of 41 days. The latter seems less probable, as hygiene measures using C. auris efficient cleaning solution have been extensively used in P0's room, including cleaning of shared material and considering that all environmental samples came back negative in culture. In addition, no other contact patient was detected positive, suggesting that no environmental source was significantly persisting.

We identified potential environmental sources of C. auris such as the bed and its mattresses but were never able to get a culture-positive environmental samples, suggesting that other routes of transmission were still plausible. These includes transmission through the hands of the healthcare workers, as previously shown (9, 12), through the sharing of material (echography machine) or very early before the first alert preventing finding the route of transmission. Indeed, it is possible that transmission could have occurred during the 7 days were both patients were hospitalized in parallel before the first recovery of C. auris in Patient 0 (Figure 1) and before an extensive and adapter cleaning procedure could be done”.

Other concerns include:
1. The manuscript still contains many phrases that are difficult to follow. Action: We shortened some phrases.

2. The authors refer to their institutional policies on C.auris surveillance in the text. These policies should be provided as supplemental material. Action: We made available these guidelines as supplemental material 1.

3. References 13-16 are various agency guidelines about C.auris infection prevention. Links to these guidelines or more specific information about where the reader can access the guidelines should be included. Reference 15 doesn't provide any source for the guideline. Action: We put hypertext links and modified references in the corresponding references.

4. The authors recommend that patients be screened at more sites than in their institutional guidelines and with culture techniques in addition to qPCR techniques without providing evidence to support this conclusion. Reply: Screening nares in addition to groin and axilla are actually recommended in our local guidelines (not in the country ones). Action: We chaged point (ii) line 211 as “(ii) The screening strategy based on one test per week during 3 weeks of axilla and groin swabs may not be sensitive enough to detect low fungal burden. Indeed, it has been demonstrated with clade IV isolates that the sensitivity of such combined specimen testing was estimated at 60% (11). As this sensitivity reach 80-90%, when additional sites including nare screening is added (11), we would recommend increasing the number of sites to be tested, including at least nares, even if we do not provide data in the present study. »
Reviewer #2 (Comments for the Author):

The authors have addressed the comments of prior review. The manuscript is easy to follow and interesting. I have the few suggestions for clarifications that would be helpful for the reader.

Were patients P0 and P1 negative for C. auris prior to the study, or untested?

**Action:** We added line 86: “but was not tested for *C. auris* colonization upon admission”. And line 116 “who was untested upon admission and negative upon screening”.

Were other patients routinely screened on the floor/unit/building?

Reply: As mentioned line 112 all the patients from the ward (n=17) were screening 3 times with culture and qPCR and were all negative.

**Action:** we change the sentence for “Seventeen contact patients during the hospitalization of P0 were tested negative with qPCR and culture upon 3 weekly testing of axillary and groin swabs as recommended [15].”

The authors suggest guideline changes may be needed. What guideline changes would they suggest and what type of cost may be associated?

Reply: line 209-210 we recommended to add nare screening in addition to groin and axilla and line 214-215, we recommended to use qPCR to obtain reliable and early results. 

**Action:** We indeed questioned costs and we are not able today to address this question. But this adding qPCR screening can be cost effective as the results come back early and that prevention procedures can be started earlier. To validate this cost effectiveness, a specific trial should be implemented. We added line XX: “We argue that qPCR can be cost-effective as early results could avoid early transmission when detected saving diagnosis, hygiene and potentially unneeded isolation procedures, but this should be evaluated in a specific study.”
August 25, 2022

Prof. Alexandre Alanio  
Institut Pasteur  
Molecular Mycology Unit  
28, rue du Dr Roux  
Bat Duclaux aile Fournneau RDC Haut  
Paris 75724  
France

Re: Spectrum01833-22R2 (First patient-to-patient intra-hospital transmission of a Clade I C. auris in France revealed after a two-months incubation period)

Dear Prof. Alexandre Alanio:

Thank you for your thorough response to the reviewer's comments and suggestions. I am pleased to accept it for publication.

Your manuscript has been accepted, and I am forwarding it to the ASM Journals Department for publication. You will be notified when your proofs are ready to be viewed.

The ASM Journals program strives for constant improvement in our submission and publication process. Please tell us how we can improve your experience by taking this quick Author Survey.

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Thank you for submitting your paper to Spectrum.

Sincerely,

Damian Krysan  
Editor, Microbiology Spectrum

Journals Department  
American Society for Microbiology  
1752 N St., NW  
Washington, DC 20036  
E-mail: spectrum@asmusa.org

Supplemental Material: Accept