Author's response to reviews

Title: Epidemic spread of ST1-MRSA-IVa in a neonatal intensive care unit, Italy

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Author's response to reviews: see over
Answers to reviewers

Reviewer: Jonathan Otter

The paper could be shorter. Perhaps in the form of a concise paper? 
Because this was not asked for by the other two reviewers, we have thought that cutting the paper was not an option

1. The premise for the study is not clear from the abstract. Did an outbreak prompt the introduction of active surveillance cultures? What other outbreak interventions were performed? Did these make an impact? 
We tried to rephrase the Methods section of the abstract to increase understandability
2. The conclusion ‘Active surveillance with the support of molecular typing is necessary to implement timely and effective control interventions.’ is not supported by the data. This is not a controlled study so this conclusion is too strong - the author's don't know what would have happened if they didn't use active screening. And other interventions could have made an impact. 
We thank the reviewer for his critical comment. We have accordingly modified the conclusion, by replacing the above sentence
3. It seems odd that all the neonates were colonised on admission. Was there a common admission source? 
No, there was not a common source

MINOR
4. Intro para 1. Puzzling to Questioning.
5. USA300 is not the 'prototypic' strain. USA400 probably pre-dates USA300 and there were other clones elsewhere. Revise.
6. 'Moreover, the light IV and V SCCmec types have been proved to be peculiar also of some epidemic HA-MRSA clones, such as ST22-MRSA-IV (EMRSA-15) and PVL-negative CA-MRSA strains have been proved to be able to cause not only community infections, but also healthcare outbreaks.' This doesn't make much sense. Revise for clarity. If you're suggesting that EMRSA-15 causes community outbreaks, then that's incorrect.
   We tried to rephrase the paragraph for clarity. Of course, we didn't intend to say that EMRSA-15 causes community outbreak
7. 'Fine-tuned' is rather colloquial.
   Yes, we have replaced it by a more scientific “highly discriminative”

Reviewer: Ralf-Peter Vonberg

Reviewer's report:

Major Compulsory Revisions
1. page 4 (MRSA surveillance):
   Why were MRSA colonized infants not physically segregated? 
   We have tried to explain why. Structural and personnel issues were considered
What exactly does "strict infection control measures" mean? 
We have added some details to clarify what we intended
2. pages 6-7 (Description of the outbreak & Infection control measures):
   I would appreciate some more data on this extraordinary event, for example
   - data on whether the deceased children died due to MRSA or due to other reasons
   This information was added
   - data on treatment and additional costs that derived from this outbreak 
   This was not an objective of our study
In our surveillance program, the environmental sampling is only included when the outbreak strain proves to belong to a species with an environmental reservoir.

Hand hygiene was monitored by direct observation, but until now has not been documented.

Minor Essential Revisions
1. page 4 (Setting):
   add "weeks" to mean and ranges of gestational ages
   This was done
2. page 5 (Laboratory methods):
   Reference #7 is rather old (from 1966); an update might be possible.
   This was done. The 1966 reference was Bauer & Kirby!
3. page 7 (Infection control measures):
   Did actually hand washing take place or was it rather hand disinfection?
   Hand disinfection. Done!
4. page 7 (Infection control measures):
   Were face masks worn by staff (as this is recommended by the SHEA guideline: Muto CA et al. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of Staphylococcus aureus and enterococcus. Infect Control Hosp Epidemiol. 2003;24:362-386)?
   Face mask were worn. This was added
5. page 8 (Discussion):
   "ST1-MRSA carriage of staff in the NICU was thought to be unlikely as no further … cases … were detected after the end of the outbreak period." May I suggest rephrasing this sentence as per definition no new cases should occur if an outbreak is successfully terminated? Did the authors think of a situation in which they would change their mind and in fact start screening of HCWs? What would they do with staff that was found being positive?
   Yes, we agree about the apparent inconsistence of the sentence. But we intended to say that an interruption of the transmission occurred without interventions on HCWs. At this time, we didn’t change our mind and we are still not practicing screening (and decolonization) of HCWs
6. table 1:
   Case #3 got admitted on May 9th and found MRSA positive one day later already. That is a rather short time frame for nosocomial pathogen acquisition. Is there any explanation or observation that could explain this?
   Yes, this is quite distant from the traditional definition of nosocomial acquisition. However, literature shows that MRSA colonization can occur very early after admission (see ref. 21)

Reviewer: Linda K. McDougal

Reviewer’s report:

Purpose of the study:
Identify MRSA isolates from a NICU outbreak (MLST)
Characterize isolates by genetic traits and related ness (MLVA)
Review the characteristics of the neonatal cases and their outcomes
Investigate the route of entry and transmission of MRSA in the NICU.
Background: Reference 4 doesn’t state the frequency of USA300 isolates in Europe.
Are the methods appropriate and well described?
**Minor Essential Revisions:**

The authors should have a clear separation of the methods and the results. I'm not sure if ‘Description of the outbreak’ falls under methods or results.

We agree with the concern of the reviewer, but the content of the paragraph is more consistent with the Results section, in our opinion. Moreover, some previous reports with a similar content include the description of the outbreak at the beginning of the results as we did.

Under MRSA surveillance, an infant was considered a case of infection if the infant had clinical signs and symptoms requiring antimicrobial therapy. Was there an isolate obtained from these ‘cases’?

Yes, the isolate from the first patient was from a blood culture (sepsis).

Laboratory methods: State the quality control strains used for disk susceptibility testing?

We have added the quality control strains of *S. aureus*.

On page 6 of outbreak description, MRSA was isolated from an axillary skin swab. However, in the discussion, it’s stated that the nares was the only surveillance sampling site.

As we have reported, our MRSA surveillance protocol includes only weekly nasal swabs. The axillary swab was done because of a dermatitis. So, it was considered as a clinical sample.

**Fig.3.** What is ETT culture?

Sorry for the double T. It was an endotracheal tube (ET) culture.

The index case (Apr.5) does not appear to be the same as case 1 in Fig. 3?

According to the standard epidemiological definitions, we have labeled as the index case the MRSA patient who first was detected by the surveillance program. However, we have arranged a revised Table 1, where the cases are listed in the same order than Fig.3. This, according with the referee’s observation, avoids any misunderstanding.

From the data in Fig. 2 all MRSA isolated during the outbreak dates were not identified as ST1. Some of the isolates were subsequently identified as ST22. How was this data handled?

Yes, as we have reported, the NICU under study is experiencing an endemic circulation of ST22-MRSA-IVa, that has proved to be resistant to all the attempts to eradicate the MRSA strain (including screening and decolonization of HCWs). However, we have easily and quickly differentiated the two strains by routinely applying MLVA.

Infection control measures: Were new and improved infection control measures applied to infants colonized with ST22 MRSA isolates? Was hand hygiene observed regularly to ensure that staff were in compliance?

Some more details about hand hygiene and monitoring have been added.

**Major Compulsory Revisions:**

One of the purposes of the study was to review the neonatal cases and their outcomes. Table 1 lists ‘outcome’ as ‘discharged’ or ‘dead’. There was no mention of outcome due to infections caused by ST1 MRSA in the discussion.

Some more information about the outcome of the MRSA sepsis case was added.

The NICU in the study had been experiencing an on-going endemic problem with ST22 MRSA for over 2 years, prompting the implementation of ‘strict infection control measures’. Meetings of laboratory personnel during the ‘outbreak’ of ST1 MRSA identified the likely cause of transmission and the major driver of the dissemination of the ST1 MRSA among infants as the hands of the health care workers. No additional factors were identified. Screening of healthcare workers was not in place when the index case was admitted; nor was it implemented during the 3 months of the outbreak. There was no data to indicate that subsequent cross-transmission occurred via the hands of the HCW as was suggested in the discussion.

Yes, we have accepted the criticism of the reviewer and we have accordingly modified the sentence by saying that it was the more likely explanation.

Are limitations of the work clearly stated?

Although there was much discussion about the pros and cons of screening HCWs in the discussion, I feel that the lack of screening of HCW was a large limitation of the study.

We have acknowledged in the revised version that lack of HCWs screening was a limitation of the study. Moreover, we have introduced a paragraph about the limits of our study, by taking into account the observations of all the reviewers.
During an outbreak, infants should be screened for MRSA on admission, as well as weekly, until evidence suggests a halt in transmission.

We accept the criticism of the reviewer, but *a posteriori* the only chance we have is to acknowledge this as a limit of the study.