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LETTER

Diagnosis of Acute Q Fever in a Patient by Using Metagenomic Next-Generation Sequencing: A Case Report [Letter]

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Dear editor

We are very interested in and much appreciated the case report made by Wang et al[1] about establishing Q fever diagnosis with the help of metagenomics tools. However, we think that a few points should be addressed pertaining to potential bias that may arise from each step of metagenomics workflow and its interpretation.

First, metagenomics captures not only living micro-organisms but also fraction of genetic materials from dead microorganisms which still remain in host body and additional confirmatory methods such as propidium monoazide (PAM) should be performed.[2] Hence, it is possible that the presence of *Coxiella burnetii* could have resulted from earlier infection before the patient got bitten by the tick and developed clinical symptoms. Identification of certain pathogens from the metagenomics data is very tricky since we have to consider the composition of microbial community and its interaction with the host and their surroundings.[3] Therefore, the investigators should take samples from the environment in which the patient had worked, ie, in the farm, pigs, co-workers who had similar cases if any and so forth. Metagenomics sequencing for each of these can be performed and the researchers should compare the results with those from the patient in order to see if there is any intertwined relationship.

Second, despite wide range of microorganisms incorporated in the database and considerably high relative abundance of *Coxiella burnetii* reads, one should always keep in mind that diagnosis of Q fever itself is difficult and in most cases, exclusion of other differential diagnosis such as tick-borne diseases must be carried out. Q fever cases are also mostly asymptomatic and unspecific if any symptoms occur, so other possible illness with similar clinical manifestations cannot be excluded.[4] Unfortunately, the authors did not provide information on whether they retrieved complete genome sequence of *Coxiella burnetii* from their reads, whether they had performed normalization and concentration matching for DNA as well as RNA samples and whether they tracked down further the remaining unidentified reads as these may affect the result interpretation.[3,5]

Last but not least, we also noticed that the investigators had given piperacillin-tazobactam, which is a broad-spectrum antibiotic, and levofloxacin before they gave tetracyclin. The administration of these drugs can affect the metagenomics results but most importantly should be done after the evidence of metagenomics has been obtained. The authors also did not mention whether they already checked the resistance profile for notable microorganisms, for example by using ResFinder database, from sequences they found in the metagenomics data.[6] The fact that the patient still developed low-grade fever after taking tetracyclin may rise concerns on unspecific infection and/or pathogen other than *Coxiella burnetii*. The take-home message is that careful interpretation of metagenomics analysis results should be made especially with regard to diagnostic identification of an infectious agent and its implication on rational antibiotic use in the wake of antimicrobial resistance issue.

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Author Contributions

FD acts as the main contributor from conceptualization, analysis to final draft. SSM and AN helped in the early draft preparation and discussion. All authors have agreed on the journal to which the article will be submitted, given final approval of the version to be published and agreed to be accountable for all aspects of the work.

Disclosure

All authors declare that they have no conflicts of interest in this communication.

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