Ethical assessment of 8 papers published by Elsevier and the American Society of Microbiology by researchers from the IHU Méditerranée Infection of the University of Aix-Marseille (France)

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1. The mandate

On June 30, 2022, the President of the University of Aix-Marseille, Prof. Eric Berton, mandated the aforementioned experts to assess potential ethical issues associated with 8 papers for which the majority of authors were affiliated with the IHU Méditerranée infection. These papers were listed as follows:

Elsevier:

International Journal of Infectious Diseases

1. "Risk factors for symptoms of infection and microbial carriage among French medical students abroad" *Int J Infect Dis.* 2020 Nov; 100: 104–111

American Society for Microbiology (ASM) :

Journal of Clinical Microbiology

2. "High Prevalence of Mycoplasma faucium DNA in the Human Oropharynx", https://doi.org/10.1128/JCM.02068-15
3. "Clostridum scindens is present in the gut microbiota during Clostridium difficile Infection: a Metagenomic and Culturomic Analysis" https://doi.org/10.1128/JCM.01663-17
4. "Passive Filtration, Rapid Scanning Electron Microscopy, and Matrix-Assisted Laser Ionization-Time of Flight Mass Spectrometry for Treponema Culture and Identification from the Oral Cavity" https://doi.org/10.1128/JCM.00517-19
5. "Fluorescence In Situ Hybridization (FISH) and Peptide Nucleic Acid Probe-Based FISH for Diagnosis of Q Fever Endocarditis and Vascular Infections" https://doi.org/10.1128/JCM.00542-18
6. "Detection of a knockdown resistance mutation associated with permethrin resistance in the body louse Pediculus humanus corporis by use of melting curve analysis genotyping. https://doi.org/10.1128/JCM.00808-12

Antimicrobial Agents and Chemotherapy

7. "Abnormal weight gain and gut microbiota modifications are side effects of long-term doxycycline and hydroxychloroquine treatment." https://doi.org/10.1128/AAC.02437-14
8. "Vitamin D and Prolonged Treatment with Photosensitivity-Associated Antibiotics." https://doi.org/10.1128/AAC.01969-13

The scope of the mandate is limited to issues related to the review of those papers by the proper ethics committee and excludes explicitly technical aspects of those studies. Depending on the papers, the questions to be addressed were either raised by readers directly to the publisher (American Society for Microbiology) or by the authors asking the publisher (Elsevier) to reply to accusations published on Pubpeer. Accordingly, this assessment will mainly focus on two elements of the ethical review process: first whether the research protocols at the origin of the listed papers were submitted to the correct research ethics committee according to the recognized ethical principles and the French law and, second, whether the ethical review process was in conformity with those ethical and legal requirements.

2. Ethical principles, applicable law and regulations: Research Ethics Committee (REC)

2.1. A universal principle of research ethics

According to paragraph 23 of the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects adopted in 1964 and last revised in Fortaleza (Brazil) in 2013 (hereafter the Declaration of Helsinki, DoH):

> *"The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this".*

The requirement of an ethical review by an independent ethics committee prior conducting research involving human participants was already introduced in the 1975 revision of the Declaration of Helsinki at the 29th WMA General Assembly in Tokyo.

It is also explicitly required by Guideline 23 of the 2016 CIOMS International Ethical Guidelines for Health-related Research involving Humans (hereafter the CIOMS Guidelines):

> *"All proposals to conduct health-related research involving humans must be submitted to a research ethics committee to determine whether they qualify for ethical review and to assess their ethical acceptability, unless they qualify for an exemption from ethical review (which may depend upon the nature of the research and upon applicable law or regulations). The researcher must obtain approval or clearance by such a committee before beginning the research."*

Those guidelines replaced the 2002 CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, which Guideline 2 contained a similar rule as did all past versions of the CIOMS Guidelines starting with the first 1982 version.

In the field of drug trials, the approval or favorable opinion of the concerned Research Ethics Committees (hereafter REC) (designated in the ICH-GCP as Institutional Review Board (IRB) or Independent Ethics Committee (IEC)) is also required before initiating a study. Chapter 3 of the 2016 ICH International Conference on Harmonization - Guideline for Good Clinical Practice E6(R2) provides detailed guidance on the responsibilities of IRB/IEC, their composition, functions, operations, procedures and records. Those rules remain unchanged since the original 1996 ICH-GCP.

The 2013 WMA Declaration of Helsinki specifies that medical research involving human participants includes research on identifiable human material and data. The 2016 CIOMS Guidelines have similar broad understanding on what is covered by this notion. As stated in its preamble:

> *"The term "health-related research" […] refers to activities designed to develop or contribute to generalizable health knowledge within the more classic realm of*

research with humans, such as observational research, clinical trials, biobanking and epidemiological studies".

On a research ethics perspective, unequivocally, a medical research project involving human participants cannot start **before** having obtained the authorization or favorable opinion of the concerned independent REC, regardless if this study is interventional or based exclusively on health data or human biological material collected for other purposes, such as diagnostic, therapy or prevention.

Of importance for this expertise, the Declaration of Helsinki makes explicit reference to "*the laws and regulations of the country or countries in which the research is to be performed*". The CIOMS Guidelines and the ICH-GCP also refer to the national laws and regulations on that matter. This is therefore necessary to analyze the French law on the role and responsibilities of RECs. But before, it is worth reminding the requirements from the scientific journals concerning the respect of ethical standards in the conduct of research involving human participants.

2.2. A requirement from scientific journals

Obtaining approval from the competent REC is not only a general ethical obligation for researchers in biomedical sciences, especially physicians and healthcare professionals, as part of their professional ethics standards, it is also a specific requirement according to the scientific journals such as the ones where the evaluated papers have been published. For instance, in the author's information, the International Journal of Infectious Diseases explicitly refers to the WMA Declaration of Helsinki "for experiments involving human". The Journal of Clinical Microbiology is also referring to the WMA Declaration of Helsinki through the Publishing Ethics Checklist of the American Society for Microbiology. This checklist includes a specific requirement concerning REC: "Approval or waiver has been granted by the relevant authority (e.g., Institutional Review Board). This approval is mentioned in the Materials and Methods section of the manuscript (or at the end of the text for shorter article types: e.g., Announcements, Short-Form Papers, etc.)". The Antimicrobial Agents and Chemotherapy being also a journal of the American Society for Microbiology, the same rules apply to it.

2.3. A French legal obligation

Obtaining the prior approval or favorable opinion of the concerned REC before starting research involving human participants is not only an ethical obligation according to professional ethics standards and scientific journals' standards, it is also an obligation based on the applicable law in most countries in the world. France is no exception about this. The first French law on biomedical research involving human participants is the "Huriet-Serusclat law"[1] adopted in 1988 and implemented in 1991 with the creation of the Committees for the Protection of Human Beings Involved in Biomedical Research (CCPPRB) which became the Committees for the Protection of Persons (CPP) in 2004. In 2012, a new law was adopted: the "Jardé Law"[2], which came in force in 2016 in replacement of the "Huriet-Serusclat law".

[1] Loi n° 88-1138 du 20 décembre 1988 relative à la protection des personnes qui se prêtent à des recherches biomédicales.

[2] Loi n° 2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine.

As a principle, all research projects which fall under the law should be reviewed by an official Committees for the Protection of Persons (CPP). The Jardé law differentiates 3 types of research involving human subjects:

1. interventional research including an intervention on patients which is not justified by their usual treatment.
2. interventional research, which does not concern medicinal products and only entails minimal risks and constraints.
3. non-interventional research including one or multiple acts or proceedings devoid of listed risks.

Only those three categories of research involving human participants must be submitted for evaluation to the competent CPP.[3] Concerning the competent CPP, the law was changed on July 1, 2014. Before this date, the application for ethical review according the law was to be submitted at one of the regional CPP where the researcher conducted their study. For the IHU Marseille Infection, the competent CPP was the CPP Sud Méditerranée I. Since July 1, 2014, the application for review is to be made at the national level with a procedure that attributes each protocol at random to one of the available CPP in France, thus limiting the risk of conflict of interests.

For research that are not interventional and do not require the collection of health data or biological material specifically for research purpose, they are not considered to fall under the national law on research involving human participants[4]. The approval by the competent CPP is not required. Yet the potential participants must be informed about the re-use of their data and biological samples for research purpose and have a right to refuse. A written consent is not compulsory but their objection must be respected.

Those projects must also be in conformity with the EU 2016/679 General Regulation on Data Protection (GRDP) as well as the French Law Informatics and Freedom of 1978 (Loi Informatique et Libertés). Article 66 of this law distinguishes two situations:

1. the research follows a methodology of reference validated by the CNIL (Commission nationale de l'informatique et des libertés, French Data Protection Committee) or
2. the project is not following such methodology of reference.

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[3] See S. Leymarie et al. Ethical and legal considerations in non interventional health clinical trials in the French context. *Contemp Clin Trials Commun*. 2022 Jul 2;28:100955. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9287146/. E. Toulouse et al. French legal approach to clinical research, in Anaesthesia Critical Care & Pain Medicine, Volume 37, Issue 6, December 2018, Pages 607-614. https://doi.org/10.1016/j.accpm.2018.10.013. P. Amiel, C. Dosquet, Comité d'évaluation éthique de l'Inserm (CEEI), Guide de qualification des recherches en santé [A qualification guide for health research], Inserm, 2021. https://comite-ethique.cnrs.fr/wp-content/uploads/2021/05/Inserm_GuideQualifCEEI_2021mai.pdf

[4] Article R.1121-1 3° du Code de la santé publique : « Ne sont pas des recherches impliquant la personne humaine au sens du présent titre les recherches ayant une finalité d'intérêt public de recherche, d'étude ou d'évaluation dans le domaine de la santé conduites exclusivement à partir de l'exploitation de traitement de données à caractère personnel mentionnées au I de l'article 54 de la loi n° 78-17 du 6 janvier 1978 modifiée relative à l'informatique, aux fichiers et aux libertés et qui relèvent de la compétence du comité d'expertise pour les recherches, les études et les évaluations prévu au 2° du II du même article. »

In the first case, a simple declaration to the CNIL is sufficient. In the second case, according to paragraph 2 of article 72 of the Loi informatique et Libertés[5], the « Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé (CESREES) » can be requested to evaluate if the project presents such a public interest that it can be authorized.

The question whether some of the papers that are the subject of the present review should have required such an authorization from the CNIL goes beyond the requested expertise. It will therefore be left aside. We will concentrate our analysis on the question whether a research project falls under the national law and should have therefore been reviewed by the competent CPP or not.

The IHU Méditerranée Infection is aware of this distinction. By creating an internal research ethics committee, since at least 2008, it has formally recognized the difference between its general obligation in terms of research ethics and its legal duties based on the Jardé Law and the previous French laws on the protection of human research participants. According to its internal regulation, this ethics committee « aims at allowing researchers who are not working in the field of competence of CPP [namely under the national law], to obtain the opinion of an ethics committee, for a publication or obtaining a financing."[6] This role of the internal ethics committee remains unchanged in the 2022 version of the internal regulation, with the same wording since 2008. Such internal research ethics committee is not contrary to the French law and is ethically acceptable to the extent that is operates in conformity with professional ethics standards and scientific journal standards.

3. Overview of the concerned papers and the raised ethical issues

The 8 analyzed papers include each a section or a sentence on ethics indicating that the research project had received ethical clearance, specifying sometimes which ethics committee issued it (CPP or internal ethics committee) and providing a reference of the decision. Some papers also mention whether informed consent was obtained from all participants (2) or, supposedly when it was not required by law (1). The issue of informed consent is not addressed in the remaining 5 papers, but for those submitted to the competent CPP, it can be deducted from the provided decisions that an Information and Consent Form (ICF) was included in the documents evaluated by the CPP. We will come back to this in the discussion.

In this section, following the list from the mandate and based on the documents provided to us, we will briefly address the questions as they were submitted to us by the University of Aix-Marseille in response to the publishers' concerns.

In terms of methodology, we mostly used the documents provided by the University of Aix-Marseille. But we also look for corresponding articles in scientific journals when there was a doubt on the nature and scope of the REC's decision, either from the CPP Sud Méditerranée

[5] « Le comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé peut se saisir ou être saisi, dans des conditions définies par décret en Conseil d'Etat, par la Commission nationale de l'informatique et des libertés ou le ministre chargé de la santé sur le caractère d'intérêt public que présentent les traitements mentionnés au premier alinéa du présent article. »

[6] « … il a pour vocation de permettre aux chercheurs qui ne relèvent pas du domaine de compétence des CPP, d'obtenir l'avis d'un comité d'éthique, en vue d'une publication ou de l'obtention d'un financement » (Comité d'éthique, Institut fédératif de recherche 48, Règlement intérieur (2008).

I for the studies falling under the Jardé law or from the internal ethics committee of the IHU for the others. All the articles identified in this process are cited below.

3.1. Paper 1 (International Journal of Infectious Diseases)

[redacted]

A. Facts

In the study design, this research is described as a "monocentric prospective cohort survey was conducted over two years (2018–2019) among medical students from the Faculty of Medicine in Marseille, France, who were planning to participate in an internship abroad during the summer". It included the completion of an inclusion questionnaire, "including demographic data, history of chronic illness, intended travel dates, and destination". It also involved self-sampling procedures from the participants before and after their travel. For that purpose, they "were given two sets of "pretravel" and "post-travel" kits, which contained questionnaire and sampling equipment (commercial rigid cotton-tipped swab applicators and viral transport media). They were also instructed how to self-collect samples, as follows: three cm in the nostril, five turns on the post wall of the pharynx, five streaks for respiratory samples; rectal samples were collected using two methods: rectal self-sampling when having a bowel movement, three centimeters through the anus, gently rubbing the inner walls of the rectum several times or stool collection after emission; vaginal samples were collected by placing the swab about three centimeters into the vagina and gently rubbing the inner walls several times, avoid touching the skin and vulva with the swab. Samples were self-collected using commercial rigid cotton-tipped swab applicators (Medical Wire & Equipment, Wiltshire, UK) and placed in viral transport media (Sigma Virocul1) for further processing at our laboratory".

In the "ethics" section, the authors stated: "The protocol was approved by our Institutional Review Board (2019-006). It was performed following the proper clinical practices recommended by the Declaration of Helsinki and its amendments. All participants gave their written informed consent".

B. Ethical considerations

This research is correctly identified in the paper as a "prospective study". In principle, it implies that the data and the biological samples needed for research are collected specifically for that study. In consequence, this project falls under the French law on the protection of human participants, namely the Jardé Law at the time the project was designed and conducted. The project should have therefore been submitted to the competent CPP **before** recruiting the first participants.

However, this project was not submitted for authorization to the competent CPP, and the authors indicated that they obtained an approval from their internal ethics committee (designated as "our Institutional Review Board) in 2019, thus explicitly **after** the study had started or even was completed.

According to information available online which authenticity could not have been verified (https://pubpeer.com/publications/AFBB22B9F05E72187917AE5AEA9957#3, last consulted on December 28, 2022), the authors specified about this:

"During the submission of the articles (in 2019), we have requested from the IHU Ethics Committee a retrospective ethics approval, only to answer to the possible requests from the

medical journals. The ethics approval was favorable under the condition we get a CPP approval first. But this answer from IHU Ethics after approval the last patient included of the medical students in 2019. At this point, the CPP request was pointless as the study was already completed".

The recognition by the authors that they have submitted their project to the internal ethics committee retrospectively is irrelevant in any case as according to their own statement in the paper, the eventual authorization came only after the start of the study. Although we were not given access to the decision 2019-006 from the internal ethics committee, it does not affect our evaluation as the authors should have in any case submitted their project to the competent CPP and not to the internal ethics committee.

Whether the reference to the cited decision 2019-006 is accurate or not, the article cannot be deemed formally in conformity with the Declaration of Helsinki and the French law and regulations. First, according to the law, the project must have been submitted to the competent CPP. Second, the approval of the CPP must have been obtained before the recruitment of the first participant as both a legal and an ethical principle.

3.2. Paper 2 (Journal of Clinical Microbiology)

[redacted]

A. Facts

According to the abstract, "Mycoplasma faucium has recently been associated with brain abscesses and seems to originate from the mouth. We evaluated its prevalence by quantitative real-time PCR (qPCR) in the oropharynxes of 644 subjects and found that 25% harbored M. faucium, probably constituting the gateway for entrance of the bacteria into cerebral abscesses". Concerning the recruitment process, it is specified that: "Between January 2013 and December 2014, 644 people were enrolled on a voluntary basis into four different cohorts of patients. Of these patients, 293 presented with tonsillitis, 23 presented with meningitis, 110 presented with acute diarrhea, and 218 were pilgrims sampled before departing from Marseille, France to Mecca".

In terms of ethical concerns, the authors mentioned that "All of the cohorts were approved by our local ethics committee under numbers 1301 (tonsillitis cohort), 1303 (meningitis cohort), 1305 (diarrhea cohort), and 1356 (pilgrims' cohort) and by the French National Drugs and Health Products Agency under numbers 2012-A01593-40, 2012-A01591-42, 2012-A01590-43, and 2013-A00961-44, respectively. Written informed consent was obtained from all participants".

B. Ethical considerations

According to the description of this project, it combines 4 cohort studies which are prospective in nature. Yet it cannot be excluded that the samples were collected during ordinary patients' care for diagnostic purposes for the 3 first cohorts. Concerning the pilgrims, the reason to collect pharyngeal swab is not specified but seems to be exclusively for research purpose as it can be deducted from other studies. In that case, the study should have been submitted to the competent CPP. The expression "our local ethics committee" in the paper is too vague to determine whether the authors are referring to the competent CPP or the internal ethics committee of the IHU. Yet, we have received copies of corresponding

decisions of the CPP Sud Méditerranée I for the tonsillitis cohort (2013-1301), the meningitis cohort (2013-1301) (sic, see below) and the diarrhea cohort (2013-1305). For this research, the situation is clear and seems to be in conformity with the Declaration of Helsinki and the French law and regulations.

It should be pointed out that the CPP Sud Méditerranée I attributed the same reference number (2013-1301) to two different cohorts, tonsillitis and meningitis. It is most likely a mistake as a closer look at the decision shows that the first one refers to a project with the EudraCT number 2012-A01593-40 and was finalized on February 5, 2013, while the second one refers to a project with the EudraCT number 2012-A01591-42 and was finalized on January 31, 2013. Interestingly, there is another project with the cohort meningitis for which a substantial amendment was submitted to the CPP on March 23, 2015 with the reference “ID RCB: 2012-A01591-42 N° d’ordre 2” which seems to correspond to the original meningitis cohort number (EudraCT number 2012-A01591-42). As the reference of the CPP 2015 decision is “13 03 MS 2”, this could indicate that the original 2013 decision of the CPP was indeed “2013-1303” as cited in the paper. This error does not have real ethical consequence, but it may well have its origin on the side of the CPP. In view of the delimitation of our mandate, they are no reason to elaborate any further on this issue.

The case of the pilgrims’ cohort is more complex. There is no explanation in the paper that could justify why it should not have been submitted to the CPP Sud Méditerranée I as the other cohorts. It may even be the case that this cohort study has indeed obtained the favorable opinion of the competent CPP, but the decision 1356 cited in the paper was not provided. In fact, according to an email by the American Society for Microbiology to the University of Aix-Marseille, it seems that a different procedure was followed for that study. A reader complained that the pilgrims’ cohort was authorized by a decision on the project 2013-A00961-44 issued by the University of Aix-Marseille on July 23, 2013. The complaint speaks about IRB and a decision of the University, with no reference to the CPP.

Interestingly, we found references in several papers, including recent ones, to a decision of the Aix-Marseille University institutional review board (23 July 2013; reference No. 2013-A00961-44) that seems to cover the same pilgrims’ cohort and which seems also to correspond to the reader’s complaint to the American Society for Microbiology, namely:

[redacted]

None of those papers mentions a decision from the CPP Sud Méditerranée I. The November 2014 paper (Emerg Infect Dis. 2014;20(11):1821-1827) is the most explicit on how the recruitment and the collect of the samples were organized: “Pilgrims who planned to participate in the 2013 Hajj were recruited on September 15, 2013, at a private specialized travel agency in Marseille, France, which organizes travel to Mecca. […] In this prospective cohort study, participants were sampled and followed up before departing from France (on October 2, 2013) and immediately before leaving Saudi Arabia (on October 24, 2013). Upon inclusion in the study, participants were interviewed by Arabic-speaking investigators who used a standardized pre-travel questionnaire that collected information on the demographic characteristics and medical history of each participant. A post-travel questionnaire that collected clinical data and information on vaccination status and compliance with preventive measures was completed during a face-to-face interview 2 days before the pilgrims returned to France by a single investigator who joined the pilgrims after the Hajj”. It is added that: “The study protocol was approved by the Aix Marseille Université institutional review board (July 23, 2013; reference no. 2013-A00961–44) and by the Saudi Ministry of Health Ethical Review Committee”.

As mentioned in the above citation, this is prospective cohort study and, as such, falls under the French law on the protection of research participants. Therefore, it should have been submitted to the competent CPP as were the tonsillitis cohort, the meningitis cohort and the diarrhea cohort (see above). Based on the available evidence, this paper could not be deemed formally in conformity with the Declaration of Helsinki and the French law and regulations.

3.3. Paper 3 (Journal of Clinical Microbiology)

[redacted]

A. Facts

As described in the paper: “With the objective of studying the gut microbiota in relation to C. difficile infections (CDI), we analyzed 30 stool samples from patients with CDI by metagenomics. […] We also analyzed 27 stool samples from healthy adults […] In parallel, as a part of a large-scale culturomic study, we analyzed six fresh stool samples from CDI patients”. It is also specified that “This study was approved by the ethics comity (sic) of the IHU Méditerranée Infection under number 2016-011 ».

The decision 2016-011 of the internal ethics committee was provided, including the information and consent form (ICF) given to the participants. Interestingly, the ICF specifies that:

«Concrètement, pour réaliser cette étude, le médecin qui vous prend en charge vous donnera un pot de prélèvement ou un écouvillon. Les prélèvements qui vous seront demandés seront non invasifs (pot de selles, urines, crachats et/ou écouvillon cutané, auriculaire, nasal, pharyngé). En dehors de ce/ces prélèvement(s), cette étude n'entraînera AUCUN geste médical ou intervention supplémentaire. […]

Comme tous les projets de recherches biomédicales, conformément à la loi n°2004-806 du 9 aout 2004 relative à la politique de Santé Publique (articles L1121-1 et L1126-6 du code de santé publique) :

- Cette recherche a obtenu un avis favorable du comité de protection des personnes (CPP) de l'IHU Méditerranée Infection
- … »

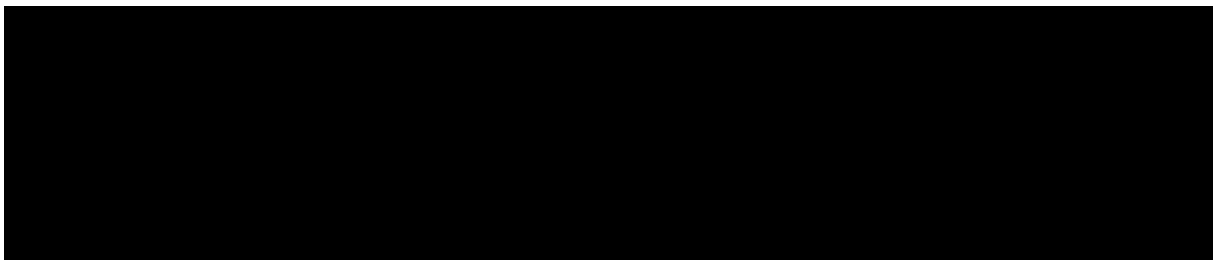
B. Ethical considerations

Concerning the 30 patients suffering from CDI, the paper does not specify whether the study used samples collected during their care, or only for research purpose. For the 27 healthy volunteers, there is no question about this. Yet, at the light of the ICF, there is no doubt about the fact the stool samples were specifically collected for research purpose ("**En dehors de ce/ces prélèvement(s),** cette étude n'entraînera AUCUN geste médical ou intervention supplémentaire" (our emphasis). This project therefore falls under the French law on research participants protection as it is explicitly recognized in the ICF. It should have been submitted to the competent CPP. As it was not the case, this article cannot be deemed formally in conformity with the Declaration of Helsinki and the French law and regulations.

It should also be underlined that the ICF is confusing by referring to the "comité de protection des personnes de l'IHU Méditerranée Infection". The term CPP designates the "official" Research Ethics Committee in the French legal terminology. For the patients and the healthy volunteers, it would have been very difficult or even impossible to realize that the study was not reviewed by the competent CPP but only by the internal ethics committee of the IHU.

Concerning the application to the internal ethics committee, the researchers did not mention whether the samples were collected specifically for this study. They did not specify the number of participants to be recruited and for which time period. There is also no indication on how the personal data and the samples of the participants will be stored in accordance with the data protection regulation and for how long.

3.4. Paper 4 (Journal of Clinical Microbiology)



A. Facts

As described in the sampling section of the paper: "Biological samples were collected from the oral cavity of 23 healthy women and 21 men between 25 and 38 years of age. […] Donors were healthy volunteers who did not have symptoms of gingivitis and/or periodontitis. Oral specimens were collected using a sterile toothbrush in the morning before brushing". It is also mentioned that "Approval (agreement no. 2016-010) was obtained from the local ethics committee of the IHU-Mediterranée Infection (Marseille, France)".

The decision 2016-010 from the internal ethics committee of the IHU was provided to us but it does not correspond to the study.

B. Ethical considerations

As mentioned above in section 2, projects requesting the collect of data and samples specifically for research purpose fall under the French law on research participants protection. Although it presents only minimal risks it should have been submitted to the

competent CPP. The fact the authors have cited a wrong reference (2016-010) for the alleged decision of the internal ethics committee is certainly concerning. Yet, it does not modify the fact this project should have been submitted to the competent CPP according to the French law. As it was not the case, this article cannot be deemed formally in conformity with the Declaration of Helsinki and the French law and regulations.

One could argue that the target of the project was not the human biological material but the detection, culture and identification of *Treponema* species and therefore that the study was not *per se* a research involving human participants. Such argument would yet miss the fact that the material from which the *Treponema* species were extracted, namely samples collected from the oral cavity of the 44 volunteers, are human biological material and that, depending on the nature of the *Treponema* species for which the volunteers were tested positive, the participants may have been affected by the diagnostic. Excluding this type of projects from the scope of research ethics, laws and regulation would be contrary to the rights and interests of the research participants.

3.5. Paper 5 (Journal of Clinical Microbiology)

A. Facts

As stated in the abstract: “We tested 23 C. burnetii-positive valves and thrombus samples obtained from patients with Q fever endocarditis. Seven aneurysms and thrombus specimens were retrieved from patients with Q fever vascular infections”. Those figures are confirmed in the results section: “Among patients diagnosed with Q fever endocarditis, we analyzed 22 (96%) valve samples and one (4%) thrombus. We also tested six (86%) aneurysms and one (14%) thrombus obtained from patients with Q fever vascular infection (Table 1)”.

The origin of the samples is specified in the materials and methods section: “We tested a series of valves and thrombus samples collected from patients with endocarditis. We also analyzed a series of aneurysms and thrombus specimens from patients with vascular infections. All these samples were received from both hospitalized patients and outpatients throughout France in our Q fever reference center in Marseille between 2014 and 2017”.

Concerning the ethical review, it is stated in the acknowledgments that “This study was approved by the ethics committee of the Méditerranée Infection foundation under number 2016-025. No informed consent was required as it was a retrospective study”. The decision 2016-025 of the internal ethics committee of the IHU was provided to us. It indicates that no samples were collected specifically for the study, but it also requested that patients be informed about the study (“Avis favorable sous réserve de l’information des patients”)

B. Ethical considerations

Based on the available information, there is no indication that the samples were collected for research purpose. It seems that they are rather left over from laboratories which used those samples for diagnostic purpose. It could therefore be considered as a retrospective study with re-use of already available samples collected in the clinical setting. In this case, the study would not fall under the French law on research participant protection and should not be submitted to the competent CPP. Yet, contrary to the statement from the authors that “No informed consent was required as it was a retrospective study”, participants had the right to be informed of the re-use of their sample for research purpose and should have been given

an opportunity to express their opposition which must have been respected. Therefore, the internal ethics committee from the IHU rightfully requested that the patients be informed prior to start the research analyses.

There is no evidence that the authors followed the requirement from the internal ethics committee. Moreover, they provided an inaccurate statement to the publisher in contradiction with the explicit opinion of the ethics committee. While an informed consent may not have been required, patients should have still been informed of the new study in order for them to validly exercise their right of opposition. As the internal ethics committee made an explicit request about this, it raises a doubt whether this rule had been respected originally or not.

Another element of concern is that the decision from the ethics committee is dated October 19, 2016, but the collection of samples for this study continued until 2017. In principle, the REC opinion for a **retrospective** study only covers the collection of data and samples obtained **before** the REC took position. Yet, one must take into account that in the general description of the project attached to the decision, it is mentioned that the collection of samples is done prospectively and retrospectively ("Détection de micro-organisme émergent ou inconnu dans les prélèvements adressés au CNR et recueillis dans le cadre des soins courant pour analyse microbiologiques **de façon prospective et rétrospective**" (our emphasis)). As the ethics committee did not react to this point, it may have considered it as acceptable according to the circumstances although this is questionable. In addition, the description does not either specify the number of participants to be recruited and for which time period. There is also no indication on how the personal data and the samples of the participants will be stored in accordance with the data protection regulation and for how long.

3.6. Paper 6 (Journal of Clinical Microbiology)

[redacted]

A. Facts

As specified in the material and methods section, "Body lice were collected from volunteers at 2 homeless shelters in Marseille before the beginning of a permethrin clinical trial. The research complied with all relevant federal guidelines and institutional policies (ID RCB: 2010-A01406-33). Alternatively, homeless individuals were given new clothes, and their louse-infested clothing was removed and brought to the laboratory for louse removal". There is no indication on the period when the volunteers were recruited and their body lice collected, except it was before the beginning of a permethrin clinical trial.

We were provided with a decision from the CPP Sud Méditerranée I (reference 10 63) that is said to correspond to this project even if the paper refers to another decision (ID RCB: 2010-A01406-33).

B. Ethical considerations

The decision 10 63 refers to a study titled: « ERADICATION DU PORTAGE DU POU DE CORPS PAR VETEMENTS IMPREGNES DE PERMETHRINE : ESSAI COMPARATIF RANDOMISE VERSUS PLACEBO EN DOUBLE AVEUGLE DANS LES POPULATIONS DEFAVORISEES DE MARSEILLE ». As there is no time frame for the study presented in the paper, it is unclear if this decision was adopted before the start of this study. In the absence of the protocol, version 3 of January 24, 2011, cited in the decision 10 63, it is difficult to verify whether this is the same study.

It may be the case that the original study for which the decision 10 63 was granted corresponds to the published paper. Such interpretation is supported by the aim of the published study, namely “to develop a rapid and robust genotyping method usable in large field-based clinical studies to monitor permethrin resistance in the human body louse Pediculus humanus corporis”, which overlaps the objective of the study cited in the decision 10 63. However, as mentioned above, the published study was conducted **BEFORE** the beginning of a clinical trial. This suggests that there were two distinct projects, namely an epidemiological study and a clinical trial. Also, the decision 10 63 mentions only a single information sheet, version 3 of January 19, 2011 and one consent form, version 1 from January 4, 2021. Even if the studies correspond to 2 phases of a single project, the information to be provided for the participants in the double-blind clinical trial to eradicate body lice by impregnating clothes with permethrin is likely different than the one needed for potential participants in a study with the aim to monitor permethrin resistance in human body lice in large-scale clinical studies. This could indicate that the decision 10 63 corresponds to a different study than the published one.

However, we also note that the paper itself does not refer to a CPP decision but mentions a decision from the internal ethics committee of the IHU: ID RCB: 2010-A01406-33. Interestingly, we found the same reference to this decision in other papers, such as:

In the last paper, the authors indicate that “this study was reviewed and approved by the Institutional Review Board and Ethics Committee of Assistance Publique Hôpitaux de Marseille (2010-A01406–33)”. There can be no doubt that this not to the competent CPP they are referring to but the internal ethics committee of the IHU. What is particularly worrisome is that in the aforementioned articles, the authors used that decision to justify inclusion of participants even more than 8 years (winter 2018) after the cited decision was granted and sometimes on topics that have, in appearance, little to do with the initial decision (e.g. on active pulmonary tuberculosis screening when the decision was regarding body lice and permethrin).

This is the responsibility of the authors to clarify the issue by providing clear evidence that they have obtained a valid approval by the competent CPP before starting the recruitment for this study. The decision provided to us does not correspond to the cited decision in the paper, and the alleged decision cited in the paper was not obtained from the proper ethics

committee. In view of the evidence at our disposal, this article cannot be deemed formally in conformity with the Declaration of Helsinki and the French law and regulations.

3.7. Paper 7 (Antimicrobial Agents and Chemotherapy)

[redacted]

A. Facts

Concerning the participants recruitment, it is specified that "We examined 82 patients, including 48 patients with Q fever endocarditis and 34 controls […] Q fever endocarditis patients were treated at an outpatient clinic (Hospital La Timone, Marseille, France) from 2008 to 2011 using a combination of doxycycline (100 mg twice a day) and OHCQ (600 mg daily) for at least 18 months according to current recommendations The controls included healthy individuals consulting as outpatients in the infectious disease unit at Hospital La Timone (Marseille, France), and these patients had not received antibiotic treatment for at least 1 year. The inclusion criteria were adult patients for whom the body mass index (BMI) value and a fecal sample were available. […] The data (gender, date of birth, clinical history, weight, weight before disease, height, antibiotic use, and significant changes in diet) were recorded using a standardized questionnaire, and no patient received antiobesity intervention during the follow-up…

It is also mentioned that "This study received ethical approval through the local ethics committee (number 10-002, 2010)". We were provided with this decision but it contained limited information. The title of the concerned study is broad: "Etude métagénomique du microbiome digestif". The number of participants is not specified, only that the study will include the use of 400 stool samples not collected for research purpose and that the patients' consent was obtained. According to an email to the American Society for Microbiology by the Prof. Philippe Brouqui, medical director of the IHU, this decision of the internal ethics committee is not the correct one. The decision which should have been cited is IFR 48 N° 07-044, which was also provided to us. The title of the study is very similar and is also broad: "Etude métagénomique de l'influence des antibiotiques sur la flore fécale". It mentions the enrolment of 15 patients and the collection of 180 stool samples.

B. Ethical considerations

The reference to a standardized questionnaire in the paper raises a doubt whether all data and samples were originally collected only for diagnostic and therapeutic purposes or if some – for instance the answers to the standardized questionnaire – were collected only for research purpose. In the second case, the study would have fallen under the French law on research participants protection and should have been submitted to the competent CPP.

If indeed all the data and samples were only collected for diagnostic and therapeutic purpose, it is correct to consider it does not fall in the scope of the law and that the approval of the internal ethics committee suffices. However, the authors have not provided the correct reference to the publisher. One could also question whether the decision IFR 48 N° 07-044 really correspond to the study in view of the discrepancy between the announced number of participants (15) with the number of patients finally included (82). Either decision (IFR 48 N° 07-044 and 10-002, 2010) is formulated in very broad terms with no limit in time and no information on the scientific hypothesis, the primary and secondary objectives, the methodology, the justification of the sample size, etc. Thus, there remains doubt whether the

first or the second decision actually covers the published study. Formally, this article cannot be deemed in conformity with the Declaration of Helsinki and the French law and regulations.

3.8. Paper 8 (Antimicrobial Agents and Chemotherapy)

[redacted]

A. Facts

For this project, “Sera were obtained from the outpatients of an infectious disease unit (Hopital La Timone, Marseille, France) who were suffering from Q fever and treated with doxycycline (100 mg twice per day) and hydroxychloroquine (200 mg three times per day) […] Overall, we tested 106 patients, including 56 with Q fever endocarditis and 50 controls”.

It is stated that “This study was performed after ethical approval by the local ethics committee (accession number 10-002, 2010)”. The corresponding decision was provided to us.

B. Ethical considerations

As for the previous study, according to a letter email to the American Society for Microbiology [redacted] this decision of the internal ethics committee is not the correct one. Yet, Prof. Brouqui did not provide an alternative decision that would cover this study. In addition, the paper does not indicate whether the sera were collected in the clinical setting or for research purpose. In the second case, the study should have been submitted to the competent CPP.

Formally, this article cannot be deemed in conformity with the Declaration of Helsinki and the French law and regulations.

4. Conclusion

In summary, after careful evaluation of all documents provided to us and additional information publicly available online, it appears that the review of the articles raises several concerns with regards to their conformity with the Declaration of Helsinki and the French law and regulation.

In most instances, the research projects should have been submitted to the competent CPP, namely the CPP Sud Méditerranée I until July 1, 2014. In one case (paper 5: Journal of Clinical Microbiology, Volume 56, Issue 9, September 2018), this was not required but there is no evidence that the authors complied with the requirement from the internal ethics committee to inform the participants and they provided a misleading statement to the publisher.

Out of the 7 protocols which were identified as falling under the Jardé Law, it could be argued otherwise for 2 of them (paper 7: Antimicrobial Agents and Chemotherapy, Volume 58, Issue 6, June 2014, 3342-3347 and paper 8: Antimicrobial Agents and Chemotherapy, Volume 57, Issue 12, December 2013, 6409-6410). Yet the authors admitted to have cited the wrong decision and did not present clear evidence that their projects were reviewed in accordance with the Declaration of Helsinki and the French law and regulation.

The fact that, in most cases, the authors demonstrated difficulties to produce the competent REC decisions related to their papers or even to cite the correct decision raises a concern on the quality assurance procedures followed in terms of data and files management. Documenting all research activities is an essential element in building the trust in science as it allows others to reproduce the same actions and also to verity that research is carried on according to the state-of-the-art. Obtaining the favorable opinion of the competent REC prior to begin a study is a fundamental requirement in research ethics (see section 2 above). The difficulties in documenting that the ethics rules have been respected raise significant questions and concerns about the procedures in place ensuring ethical practices.

As alluded to above, there are evident concerns about the governance in place at the IHU Méditerranée Infection and Aix-Marseille University concerning ethical review mechanisms and how researchers are trained, instructed and supervised when submitting their projects to the appropriate research ethics committee depending on the nature of their studies. Although we were not directly mandated to address this issue, it cannot be ignored as it has a direct impact on the evaluation of the ethical issues related to the 8 reviewed papers. Undoubtably, it is necessary to establish a clear ethics governance for the research institution and, if there are different RECs in an institution, to clearly distinguish their responsibilities and mandates.