

FEATURES



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THE RECKONING

Didier Raoult and his institute found fame during the pandemic. Then, a group of dogged critics exposed major ethical failings

With six studies published in the 2010s, French microbiologist Didier Raoult added to his already vast publication record. He and his colleagues conducted a wide range of investigations into infectious diseases and their treatments. They took stool samples from patients on long-term antibiotic treatment, looking for alterations in their gut microbiome. They swabbed the throats of pilgrims leaving France for Mecca, searching for evidence of a bacterium that causes brain abscesses. And they studied samples of heart valves and blood clots from patients with heart inflammation to refine tests for the bacteria that cause the condition.

But in January, the American Society for Microbiology (ASM) journals that published the papers announced they were retracting all six, along with a seventh by Raoult's colleagues. Aix-Marseille University had investigated the research, which was done at its affiliated Hospital Institute of Marseille Mediterranean Infection (IHU), a research hospital that Raoult led until his retirement in 2021. The investigation found the work had not been reviewed by one of France's highly regulated national ethical committees. It was therefore in violation of French law and the Declaration of Helsinki, an international ethics document that guides clinical research.

In a written statement sent to *Science*, Raoult says ASM retracted the papers without accounting for his team's rebuttals to the critiques. But to Lonni Besançon, the retractions are vindication of concerns that he and others have been voicing since Raoult and the IHU burst into the media spotlight in the early days of the COVID-19 pandemic, downplaying its severity and touting prospects for a successful treatment.

The Linköping University computer scientist and his fellow critics—a gaggle of dogged individuals, many of them academic outsiders—originally set out to challenge poor-quality research coming out of the IHU, especially the claim that COVID-19 could be treated with the antimalaria drug hydroxychloroquine (HCQ). But they soon embarked on an all-consuming attempt to raise the alarm about ethical failings in the institute's research, going back at least 15 years.

Their efforts have met with lackluster responses from France's scientific institutions, Besançon says, but the retractions are the most important consequence so far. They “confirm what we suspected,” he says. “But I am hoping that things will go further.”

Raoult says his critics are stalkers and cyberharassers who have misunderstood

how French biomedical law works. He says he's followed ethical regulations and that much of the research under fire has been on “human waste”—such as fecal matter—which is not defined as biomedical research under French law.

But the ethical failings are “not disputed” within the scientific community, says Philippe Amiel, a lawyer who specializes in human experimentation. The authorities have known about problems at the IHU for years, adds Karine Lacombe, an infectious disease specialist at Sorbonne University. If they had acted earlier, she says, “the picture of the pandemic in France would have been totally different.”

A criminal investigation of Raoult's institute is now underway. But his critics are asking why French institutions took so long to tackle systemic violations at the IHU, leaving it to a persistent group of outsiders to investigate the institute and push for punitive action. And they are wondering whether Raoult and the institute will be held to account for the wide range of lapses they have alleged.

“It's a big, big mess,” Lacombe says.

RAOULT IS BEST KNOWN for his work on rickettsia—bacteria transmitted by fleas and ticks—and his discovery of giant viruses. He has accumulated national decorations in both France and his birth country of Senegal as well as prestigious scientific awards, including the 2010 Grand Prize from the French biomedical research agency INSERM. He has published prolifically, with more than 3200 papers indexed on PubMed, and is one of the most highly cited researchers in his field.

In 2011, Raoult was selected to lead the newly created IHU in Marseille, one of six state-of-the-art research hospitals established by then-President Nicolas Sarkozy's government. Raoult's IHU, which specializes in infectious disease research, was launched with a €72 million government grant, and in 2018 it moved into an imposing new building. The institute's power is political as well as scientific, says Michel Dubois, a sociologist of science at the French national research agency CNRS: “When you open this institute—when you create a building—you need some leverage at the political level.”

As Europe began to pay serious attention to the COVID-19 pandemic in early 2020, the media wanted to know what Raoult and his institute made of the situation. “Almost every day, you were able to watch a new interview with Raoult,” says Antoine Bristielle, a social scientist at the Jean-Jaurès Foundation, a think tank. “It became



ILLUSTRATION: SARA GIRONI CARNEVALE

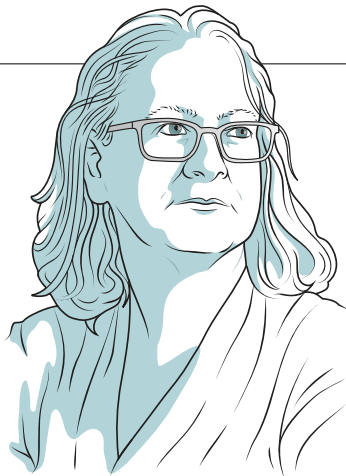
a self-reinforcing phenomenon ... the media were interested in what he was saying, so he came to be really powerful in the French population. And then, of course, the media wanted him because he was able to attract large audiences.”

In videos posted online by the IHU, Raoult is often seated in an office, wearing a lab coat, long gray hair and beard slightly unkempt. He speaks soberly and quietly, frowning slightly while delivering reassuring pronouncements: The new coronavirus has a mortality rate not too different from widespread respiratory infections; a treatment will be coming soon.

Raoult's confident statements caught the eye of Fabrice Frank, a former biologist who had left academia and become a high school math and physics teacher. By the time the pandemic hit, Frank had moved from France to Morocco, where he started an IT company and dedicated his spare time to surfing. He watched with shock when Raoult asserted—with minimal evidence, based on thinly reported research in China—that HCQ, or the related medicine chloroquine phosphate, would be an effective treatment.

Victor Garcia, a journalist at French magazine *L'Express*, saw scientists expressing skepticism about Raoult's claims on social media. He called the IHU, assuming it had more details that could counter some of the critics' concerns. But Garcia says he received a “strange” response from IHU researcher Jean-Marc Rolain. “I am a scientist,” Rolain said. “If I tell you to take chloroquine, you'll listen to me.” (Rolain did not respond to multiple requests for comment.) That was “the beginning of me asking questions,” Garcia says.

ON 11 MARCH 2020, French health minister Olivier Véran invited Raoult to join the Scientific Council advising the government on its



Elisabeth Bik, a scientific integrity sleuth based in San Francisco, first raised concerns about the Hospital Institute of Marseille Mediterranean Infection's (IHU's) work on hydroxychloroquine (HCQ) in March 2020. She went on to identify major ethical and scientific issues in dozens of IHU papers, spurred on, she says, by abuse from Didier Raoult and his supporters.

pandemic response. A few days later, Raoult and his team published a bombshell paper in the *International Journal of Antimicrobial Agents*, reporting that the IHU had found HCQ combined with the antibiotic azithromycin to be an effective COVID-19 treatment.

Although the results were preliminary and other researchers doubted Raoult's conclusions, HCQ hype surged, with then-U.S. President Donald Trump touting its promise and Raoult enthusing over it on YouTube. “Raoult was saying, ‘I understand everything, I have a solution,’ and people want that kind of information in troubled times,” Bristielle says.

Raoult's popular support bred political support, Bristielle adds. “If someone has such a presence in the media landscape, politicians have to listen to him—otherwise they will be really distrusted by the population.” On 26 March—amid strong resistance from some other members of the scientific council—Véran issued a decree allowing HCQ

to be prescribed to COVID-19 inpatients.

Scientific integrity consultant Elisabeth Bik decided to take a close look at the HCQ paper. A microbiologist by training, Bik already knew of Raoult and his reputation for prolific publication. On her blog she pointed to several problems she saw with the paper: Patients had not been randomly assigned to the treatment and control groups, which could have biased the results. She also noted that six patients out of the 26 treated with HCQ were dropped from the data—including three who were transferred to intensive care and one who died—which painted a more favorable picture of the treatment.

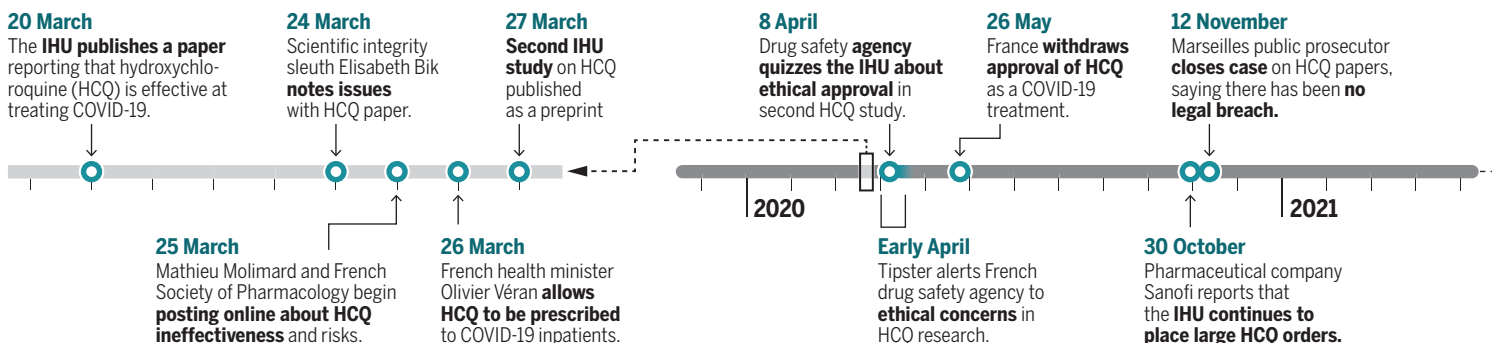
Besançon, too, was curious. He looked into the paper, which had been submitted to the journal on 16 March and accepted the next day, and noticed that one of the authors was also editor-in-chief at the journal. “So you have a very short reviewing time and editorial conflict of interest,” he says. “I just find this potentially a big red flag. But I thought, it's just one paper.” (A July 2020 editorial in the journal said handling of the paper had been delegated to an associate editor to minimize potential bias, although it noted that “some of the concerns regarding the paper's methodology were substantiated.”)

Over the next few weeks, two more IHU studies appeared, with unusually short peer-review timelines, both in a journal where one of the authors was an associate editor. One of those papers was a second study using HCQ to treat 80 “mildly infected” hospitalized COVID-19 patients; nearly all improved clinically. The study had not been reviewed by one of France's 39 Committees for the Protection of Persons (CPPs), the highly regulated independent ethics committees authorized to approve biomedical research. Instead, it had been approved by the IHU's internal ethics committee.

This was sufficient, the authors wrote,

A slow-motion downfall

Critics first raised concerns about ethical approvals for Didier Raoult's studies in early 2020, as the COVID-19 pandemic catapulted the Hospital Institute of Marseille Mediterranean Infection (IHU) to prominence. They say French authorities and journals have taken far too long to react.



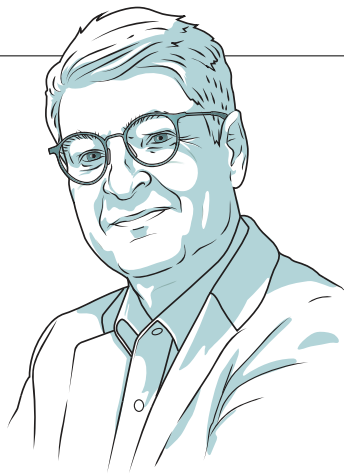
because it was a retrospective study on patients who had received normal medical care, with researchers merely looking back over their files to see how they had fared. In France, such studies are not covered by the law on research ethics, and so do not need approval from a CPP. Instead, researchers often seek approval from institutional ethics committees—which are unregulated—to supply ethical approval details to journals. But if samples are collected for both research and medical care, then the study must be approved by a CPP, Amiel says. “Concealing a prospective study as a retrospective study is a well-known temptation,” he says. Unauthorized research is a criminal offense.

The French National Agency for the Safety of Medicines and Health Products (ANSM) said it asked the IHU for evidence that the study had in fact been retrospective, and in May 2020, the agency referred the case to the French Medical Association. The Marseille public prosecutor, alerted to the case by a tipster, announced later that year that the study had been retrospective and dropped the case.

Still, those early concerns were a cue for Bik, Besançon, and others to look closely at Raoult’s substantial publication record—and to pay particular attention to ethical approval.

DESPITE THE GROWING SKEPTICISM from scientists and others, Raoult’s public support endured. A poll in May 2020 found that 30% of French people trusted him more than Véran. By June, there were more than 90 Facebook groups supporting him, according to Briestelle’s research, with a total of nearly 1.1 million members. By Christmas, supporters could buy a *santon* of Raoult—a small terra cotta figurine traditional to Provence, where nativity scenes incorporate local characters and heroes.

Meanwhile, Frank, Garcia, and other critics began their deep look into Raoult’s body of research. Bik says she focused first on images in his papers, because her specialty is detecting image manipulation. But, faced with insults from Raoult—and harassment from his colleagues and supporters—she chan-



Mathieu Molimard, a pharmacologist at the University of Bordeaux, began to counter the IHU’s claims about HCQ in April 2020. Outraged when French authorities didn’t respond to the IHU’s publication of a seemingly unauthorized HCQ trial, Molimard rallied representatives of 14 French scientific societies to sign an open letter in *Le Monde*.

neled her frustration into assessing his vast back catalog, finding more studies that appeared to lack proper ethical approval.

Garcia had also begun to scrutinize IHU papers, and in July 2021 published an investigation in *L’Express* that reported finding 17 studies between 2011 and 2020—mostly involving homeless people or refugees—that had all used the same ethical approval number, even though the studies used different methods to answer different research questions. One, for example, took nasal swabs in a homeless shelter to test the prevalence of microbes; another took sputum samples and chest x-rays from shelter residents to test for tuberculosis. (An IHU representative told *L’Express* the repeated use of the code was the result of “editorial errors.”) Again the ethical approval number came from an institutional ethics committee, not a CPP, Garcia reported.

Frank, too, had begun to dig. Stuck at home in Morocco under quarantine, he trawled Google Scholar for IHU studies that shared ethical approval codes. With his collaborators—including Besançon—he ultimately discovered 248 studies that had used the approval number “09-022,” representing a sin-

gle application to the IHU ethics committee.

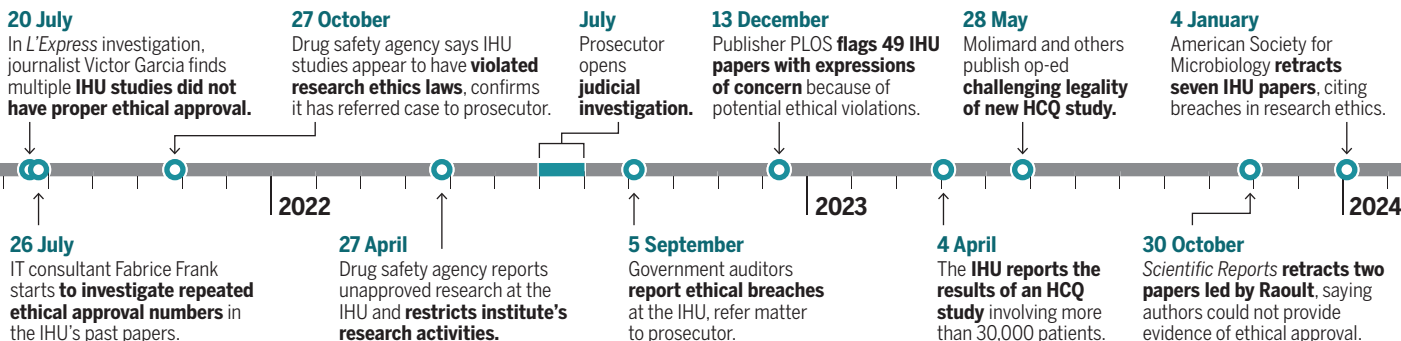
Raoult was an author on all but 10 of these 248 studies. He told *Science* it is “perfectly true” that all these papers reused the ethics approval number. But that was permissible, he says, because all involved the same kind of research: analyses of bacteria in human feces collected during standard care, or from waste. None of the research fell under French bioethics law, he says.

But Amiel says the studies describe samples taken for research purposes and not just as part of standard care, and that this type of study should “undoubtedly” be authorized by a CPP. And many of the 248 studies relied not on feces, but on other material, including vaginal samples, urine, blood, and even breast milk. Any change in research protocol should prompt a new application for ethical approval, Amiel says.

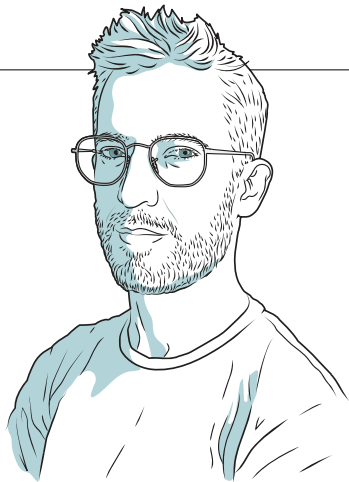
Many of the papers involved children, and nearly half of them had been conducted outside of France—largely in various African countries—with no or hazy details of whether local ethical bodies had given approval for the research, according to Frank and his collaborators. “There have been so many breaches in ethics law, for so long,” says Frank, who published the group’s findings in *Research Integrity and Peer Review* in August 2023.

Raoult says the studies relying on material other than stool samples had “supplemental favorable advice” from the local ethical committee, but that his team did not report this in its papers. The only country for which his team did not have ethical approval was Niger, he adds, which did not have an ethical approval process until 2016. He says he and his colleagues have submitted a reply to Frank’s paper, and they have asked Springer Nature—the journal’s publisher—to retract it. A Springer Nature spokesperson said, “We are aware of concerns with this paper and are investigating the matter carefully in line with our established processes.”

The fact that so many studies involved vulnerable populations, such as those living in homeless shelters, was “outrageous,”



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Victor Garcia, a journalist at French magazine *L'Express*, began to pay attention to Raoult when he enthused about the potential for HCQ as a COVID-19 treatment. Garcia covered the emerging IHU story beat for beat and published two investigations into ethical abuses there. Shortly after publication, the French drug safety agency began to inspect the IHU.



Ex-biologist **Fabrice Frank**, now an IT consultant, used his time in COVID-19 quarantine to begin compiling a database of all IHU papers that appeared to reuse ethical approval numbers. He and his collaborators identified 248 papers that used the same code, despite investigating different questions, using different samples, in different participant populations, and in different countries.



Lonni Besançon, a computer scientist at Linköping University, grew curious about Raoult's work after noticing a paper published in a journal where an author also served as editor-in-chief. He has co-authored several papers about ethical lapses and methodological problems in IHU research, and agitated for journals to investigate and retract problematic work.

Bik says. Vulnerable people may feel they have no choice in whether to participate in a research study, says Lisa Rasmussen, a research ethicist at the University of North Carolina at Charlotte. "They are not in a position to give authentic consent."

IN RESPONSE TO MEDIA ATTENTION—but more than 18 months after Bik first raised questions about ethical approvals and study methods on her blog—French authorities began inspections at the IHU. In October 2021, ANSM said it had found breaches of the law and had referred the matter to the public prosecutor, and that it was still investigating. The French government also asked two auditing bodies, the General Inspectorate of Social Affairs and General Inspectorate of Education, Sport and Research, to investigate.

Raoult says these inspections arose out of a "small conspiracy to make it appear that we were carrying out an illegal trial of treatment for tuberculosis." (According to one media report, IHU patients with tuberculosis had been given unproven treatments.) Raoult says the agencies found no such illegal trial and only three minor problems with other research projects. However, both ANSM's report, released in April 2022, and the auditing agencies' report, published 5 months later, noted that IHU patients had received unapproved tuberculosis treatment, with some suffering severe adverse effects. This might constitute a criminal offense, according to the auditing agencies.

But the reports also went much further, describing ethical concerns similar to those raised by Frank, Garcia, and others. The government auditing bodies noted that the IHU relied heavily on its internal ethics committee, "whose composition does not

sufficiently guarantee its independence and whose working methods do not allow for an informed decision." And ANSM described research projects launched without or before ethical approval, missing consent forms, and researchers who did not understand ethics regulations. They found evidence of a falsified signature on an ethical approval document for a study that asked students to provide samples—including vaginal and rectal swabs—before and after travel, to see whether they brought antibiotic resistant bacterial strains back with them.

The government inspectors also reported "widespread deviant medical and scientific practices within the IHU," including ones that blurred the line between patient care and research. For example, clinicians gathered a range of samples from each patient that would then be archived, possibly to be used in future research. When treating COVID-19 patients, clinicians conducted a range of tests, including daily PCR and other tests that "are a matter of research and not of care," the investigators reported. The institute rushed research in a "race to publish," the report says, racking up hundreds of publications each year—with more papers in lower tier journals than other similar institutions—and drawing in substantial funding designed to encourage high publication rates.

The inspectors reported that INSERM, which had helped found and run the IHU, withdrew from the institute in 2018. An INSERM spokesperson says it had found that several research projects did not meet its scientific standards. CNRS withdrew in 2016 and has had "no connection" with the IHU since 2019, according to a spokesperson. The reports did not specifically blame Raoult for these failings. But they said he

tightly held the reins of power in the institute, with testimonies from employees reporting that Raoult was "omnipresent" and the "final decision-maker," and that other managers were "in total conformity" with Raoult's views.

ANSM placed the IHU under its supervision to ensure that all future research projects were carried out with proper approval. And both the government agencies and ANSM again referred their findings to the public prosecutor. The status of that investigation is unclear, and the prosecutor, Nicolas Bessone, did not respond to multiple requests for comment. Raoult says he is "hopeful" that the cases currently under investigation will be closed soon. Cases are sometimes referred to other jurisdictions in France when there may be local conflicts of interest, says University of Bordeaux pharmacologist Mathieu Molimard, who has been criticizing the IHU's statements and research since early 2020: "We would prefer this to be seen in Paris."

DESPITE THE NOW INTENSE scrutiny of their work, in April 2023 Raoult and his colleagues published a draft paper that sent new shock waves through social media. "I fell from my chair," Molimard says. "It's the largest unethical study performed for years—in France, maybe in the world. ... It's incredible." More than a dozen scientific bodies would later agree with his assessment.

Raoult and his colleagues had analyzed data from 30,202 COVID-19 patients treated at the IHU between March 2020 and December 2021—including 23,172 who had received a combination of HCQ and azithromycin. Yet France had withdrawn the temporary permission to treat COVID-19 inpatients with HCQ in May 2020, after a paper in *The Lan-*

cet reported that HCQ was not an effective COVID-19 treatment. (This paper was subsequently retracted after the data were questioned, but a later randomized, controlled trial published by the mass RECOVERY collaboration also found no effect.)

The preprint showed the IHU had continued to prescribe the drug on a grand scale long after this, Molimard says.

Raoult says he and his colleagues decided in April 2020 to treat COVID-19 patients with HCQ “off label,” after their initial study convinced them of the drug’s efficacy. In France, as in many other countries, drugs can be prescribed for reasons outside of their normal authorization, but this off-label prescription must have medical and scientific justification, Amiel says—and “in this case, strong medical and scientific evidence have established that the prescription of HCQ to treat COVID is unjustifiable.”

The study also reported no approval from a CPP; the ethics section lists only an IHU ethics committee reference number. As they had in earlier papers, the researchers said the study was retrospective, analyzing patient data from the hospital’s information system. But Amiel says the IHU team was “highly committed to proving the efficacy of its treatment,” pointing to evidence—revealed by the government inspection—that it performed daily PCR tests to check viral levels, for instance. “It is perfectly clear that the study is based on data collected in a mixed care and research context.”

Molimard thought ANSM and the Ministry for Solidarity and Health should have reacted immediately to the publication. Aghast at their silence, he contacted a range of French societies, urging them to sign an op-ed in major French newspaper *Le Monde* calling the study “the largest ‘wild’ therapeutic trial known to date.” Fourteen scientific bodies, including the national coalition of ethics committees and the French Society of Pharmacology and Therapeutics, signed the letter, and in June 2023, ANSM announced it had once again referred the matter to the prosecutor. On 30 October, the paper was nonetheless published in the Elsevier-owned journal *New Microbes and New Infections*.

The scale of the trial is like nothing seen before, Molimard says. He points to the recent case of Jean-Bernard Fourtillan, a researcher who tested melatonin patches on Alzheimer’s and Parkinson’s patients without ethical approval. His study, Molimard says, involved approximately 300 patients: “And he went to jail.”

IN RECENT MONTHS, more blows have fallen on the IHU, beginning with the retraction of two *Scientific Reports* papers in October 2023 for a lack of evidence of ethical over-

sight in Niger and Senegal, where the studies were conducted. Raoult says the team did get ethical approval from an institutional review board in Senegal; because Niger had no ethical approval processes when the study was conducted, local collaborators confirmed the research complied with local laws, he says. A spokesperson for Springer Nature, which publishes *Scientific Reports*, says that in such cases researchers must still get ethical approval from another source, such as a university. The two studies are “part of a wider investigation concerning potential ethical issues in a number of papers,” according to the spokesperson.

PLOS journals have flagged nearly 50 further IHU papers with expressions of concern as part of an ongoing investigation, which Retraction Watch reported in December 2022. (At the time the studies were submitted, PLOS editors did not routinely ask for evidence of ethical approval, according to David Knutson, head of communications at PLOS.) In November 2023, the Marseille hospital board told the AFP news agency it “strongly condemned” the mass HCQ study; the IHU said it “shared” the hospital board’s reaction. And Elsevier announced that *New Microbes and New Infections* had opened an investigation into ethical concerns about IHU papers published in the journal. An Elsevier spokesperson did not confirm whether the “wild clinical trial” was one of the papers under investigation.

In December, the French ministers of health and research asked a disciplinary body that oversees university hospitals to launch proceedings against Raoult’s three IHU co-authors on the mass COVID-19 study—but not against Raoult, who retired in the summer of 2021.

The fight has taken its toll on the critics. They have faced not just abuse from his supporters on social media and complaints to their employers, but also the threat of legal action from Raoult, who has had multiple legal complaints bankrolled by the IHU. Raoult’s lawyer said Raoult had filed charges against Bik in April 2021 for harassment and blackmail. He has also filed legal complaints against other critics, including Lacombe; Raoult lost his case against her in November 2022. In science, Molimard says, “we are used to debate, to argument ... but we are not used to that!”

Despite the harassment, Besançon says he is undaunted and intends to continue to criti-

cize Raoult’s work. “I was raised in a really bad neighborhood,” he says. “You know when you see cars burning in France? That’s where I was ... I had to stand up for myself, to learn not to be afraid of potential bullies.” Bik, too, has no plans to stop: “I don’t really have a career he can ruin,” she says. “I’m not going to let him silence me.”

Besançon and others say France’s institutional response has been unacceptably weak. There has been “failure at every level,” Garcia says: at the health ministry; in the justice system; within the university and regional hospital board, which had oversight of the IHU; and at ANSM, which only conducted a full inspection after media investigations brought the problems to light. Journal editors have also been too slow to react, Besançon says. “More often than not, it seems that they don’t give a damn about integrity.”

The IHU, the regional hospital board, and ANSM did not respond to multiple requests for comment. The ministry of health said in a statement to *Science* that “several actions have been taken by the public authorities in response to the shortcomings observed at the IHU.”

Part of the failure lies with France’s law on research ethics, Amiel says, which is out of step with international standards. “It’s provincial,” he says. “And it’s really a problem.”

Because the law allows some human studies to proceed without ethical approval, Amiel says, similar violations are ongoing elsewhere in France, though not at the scale of the IHU’s. The best solution would be to overhaul the law, he says—but “I don’t think it’s a priority for the government at the moment.”

The close relationship between political powers and scientific institutions in France is also to blame for the foot-dragging institutional response, Lacombe says. Without external voices—like Bik, Frank, Besançon, Molimard, and Garcia—“I’m not sure that things would have moved,” she says.

Frank worries the lackluster response sends a message that there are no consequences for violations like these. “Maybe tomorrow—I hope not—we’ll have SARS-3 ... and the message sent will be, ‘Don’t worry about public health. Just show your face, say anything you want, and you will sell books, be famous, and get a lot of fans.’ It’s insane.” ■



Didier Raoult

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