Am. J. Trop. Med. Hyg., 103(1), 2020, pp. 38–40
doi:10.4269/ajtmh.19-0559

Perspective Piece

Confronting the Multidimensional Challenges of Research in the Context of Emerging Infectious Diseases in Brazil: The Example of Yellow Fever

Vivian I. Avelino-Silva,[1]* Claudia Figueiredo-Mello,[2] Luciana V. B. Casadio,[1] Ana C. S. S. Nastri,[1] Izabel Marcilio,[1] Ana F. Ribeiro,[3] Anna S. Levin,[4] and Ester C. Sabino[4]

[1]*Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil;* [2]*Instituto de Infectologia Emílio Ribas, Faculdade de Medicina da Universidade de Sao Paulo, São Paulo, Brazil;* [3]*Instituto de Infectologia Emílio Ribas, São Paulo, Brazil;* [4]*Instituto de Medicina Tropical, Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil*

Abstract. In the most recent Brazilian yellow fever (YF) outbreak, a group of clinicians and researchers initiated in mid-January 2018 a considerable effort to develop a multicenter randomized controlled clinical trial to evaluate the effect of sofosbuvir on YF viremia and clinical outcomes (Brazilian Clinical Trials Registry: RBR-93dp9n). The approval of this protocol had urgency given the seasonal/short-lived pattern of YF transmission, large number of human cases, and epidemic transmission at the outskirts of a large urban center. However, many intricacies in the research regulatory and ethical submission systems in Brazil were indomitable even under such pressing conditions. By April 2018, we had enrolled 29 patients for a target sample size of 90 participants. Had enrollment been initiated 3 weeks earlier, an additional 31 patients could have been enrolled, reaching the prespecified sample size for the interim analysis. This recent experience highlights the urgent need to improve local preparedness for research in the setting of explosive outbreaks, as has been seen in the last few years in different countries.

In the past decade, recurrent outbreaks of human sylvatic and peri-urban transmission of yellow fever (YF) have been reported in the southeast of Brazil. So far, the transmission has remained limited to sylvatic and peri-urban areas, and actual urban transmission has not been demonstrated.[1] However, the risk of urban transmission is substantial and is exacerbated by the low vaccine coverage[2] and the widespread presence of competent *Aedes* vector in urban areas.[3]

In the most recent outbreak, cases peaked in Sao Paulo, the wealthiest and most populous state in the country. Although a surge in the incidence of the disease has been noted since early 2017, beginning in January 2018 a striking increase in incidence has been detected in the metropolitan area of Sao Paulo city, and through April 2018, 501 autochthonous YF cases were officially reported.[4] Patients presenting with classic symptoms of YF were increasingly referred to tertiary hospitals in early 2018.

The clinical presentation of human YF varies widely, and severe cases are associated with rapid deterioration and high case-fatality rates.[5] The picture observed in tertiary care hospitals in our setting is no different. Besides, most patients are young and previously healthy, and the lack of a specific, efficacious treatment renders healthcare providers increasingly frustrated, with a sharp sense of tied hands. In the recent outbreak in Sao Paulo, we witnessed widespread use of therapeutic strategies without robust evidence of efficacy such as n-acetylcysteine and plasmapheresis.[6,7] Liver transplant in the context of acute liver failure due to YF was also performed in a few cases as a salvage intervention. However, this has been associated with high morbidity and mortality.[8]

Providers in Sao Paulo, Minas Gerais, and Rio de Janeiro have recently initiated the prescription of antivirals such as sofosbuvir as a tentative treatment for YF. Sofosbuvir is approved for hepatitis C virus treatment,[9] and in vitro activity against YF has been demonstrated since 2017 but made publicly available only in 2018, which may have accounted for additional delays in the development of YF treatment protocols.[10,11] Given the prior experience with sofosbuvir use with acceptable safety profile, many physicians felt comfortable in prescribing the drug despite inexistent evidence of clinical efficacy. Even so, the scientific evidence was urgently needed.

In this context, a group of clinicians and researchers in Sao Paulo initiated in mid-January 2018 a significant effort to develop a multicenter randomized, controlled clinical trial to evaluate the effect of sofosbuvir on YF viremia and clinical outcomes (registered at the Brazilian Clinical Trials Registry: RBR-93dp9n). We conceived and wrote the protocol in approximately 1 week, despite the lack of specific funds, and addressed worries from some healthcare providers who felt that a randomized trial could be unethical in this context. Regulatory steps for the protocol approval were fast-tracked as much as possible, based on our vast experience in facing the lengthy and bureaucratic procedures of medical research in Brazil. In this particular study, the approval had special urgency because of the seasonal, short-lived pattern of transmission of YF and its well-defined public health impact.

However, several intricacies in the regulatory and ethical submission systems in Brazil were indomitable even under such pressing conditions. For instance, federal regulations require protocols to be submitted electronically in a unified platform. Although the ethics review by the local Institutional Review Board (IRB) may be sufficient in some cases, approval by the National Research Ethics Committee (Comissao Nacional de Etica em Pesquisa) may be additionally required. The criteria for evaluation by the national-level committee include studies in human genetics and reproduction, studies of investigational new drugs or equipment, and also studies with international funding,

*Address correspondence to Vivian I. Avelino-Silva, Faculdade de Medicina da Universidade de Sao Paulo, Av. Dr. Eneas de Carvalho Aguiar, 470 - sala 06 - Cerqueira Cesar, Sao Paulo 05403000, Brazil. E-mail: viviansilva87@gmail.com

among others. Furthermore, the local IRB may request a revision by the national committee not grounded on any of the traditional criteria, which means that a protocol may take 2–3 months to fulfill the entire submission-to-approval process. Furthermore, this process can be protracted during holidays or summer vacations such as early January or Carnival in Brazil.

In the case of this specific protocol, despite the absence of specific criteria, the local IRB decided to send the protocol for revision by the national-level committee (CAAE 82673018.6.1001.0068). The reason for this additional evaluation was not specified. We assume that the ethical implications of a randomized YF treatment protocol were deemed to be too complex for local revision only. As a consequence, ethical approval was delayed by 3 weeks, during the peak YF season. The missed enrollments over the course of these 3 weeks were critical in delaying the minimal sample size of 60 participants estimated for protocol interim analysis.

In the days and weeks after the submission of the protocol for regulatory approval, at least six additional hospitals requested to be included in the study as new recruitment sites; however, an amendment to the protocol including the partner institutions could not be promptly submitted as the electronic submission platform only accepts amendments after the formal approval of the prior version. The local IRB at each new participant institution was not allowed to review the protocol in parallel and could only access study documents after the approval by the national committee, further delaying the evaluation and approval of the study.

After the approval of the protocol, additional logistic and operational difficulties emerged. The donation process of the study medication could only be started after formal IRB approval and lasted nine additional days. In the laboratory, we faced the usual delays for the importation of reagents, high costs, and bureaucracies in sample shipping, lack of human resources to perform bench work, and scarcity of freezer space.

Funding for this study came from aggregated seed funds available from five different laboratory groups, in addition to emergency funds made available from the state research agency (FAPESP, Sao Paulo Research Foundation).

Personnel hired to coordinate and perform study procedures had to commit to work despite a lag of 2 months or more for financial compensation.

By April 2018, we had enrolled 29 patients in the study, for a target sample size of 90 participants. Had enrollment been initiated 3 weeks earlier (i.e., 2 weeks after initial submission), an additional 31 patients could have been enrolled only at the primary institutions, Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo and Instituto de Infectologia Emilio Ribas, reaching the prespecified sample size of 60 participants for interim analysis (Figure 1).

It is important to mention that economic disparities seen across different states in Brazil also correlate with disparities in research capacity; the challenges we present here would likely be more striking had the study been conducted in other, less affluent regions of the country.

We fully acknowledge that ethical and regulatory approvals are intrinsic and essential elements for conducting medical research in compliance with the International Conference on Harmonisation—Good Clinical Practice. However, to what extent could unnecessary delays in the implementation of protocols be considered unethical, particularly in outbreak

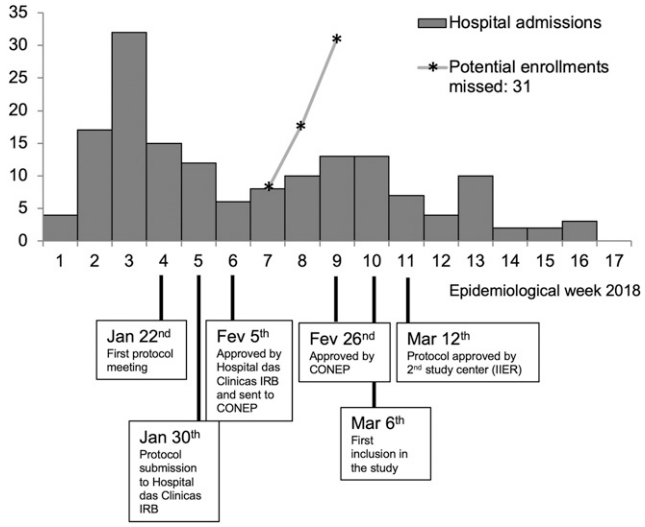

FIGURE 1. Yellow fever hospital admissions and potential enrollments missed by 2018 epidemiological weeks. CONEP = Comissao Nacional de Etica em Pesquisa—National Research Ethics Committee; IIER = Instituto de Infectologia Emílio Ribas; IRB = Institutional Review Board.

research? Late publication of new research findings, delayed regulatory approvals, protracted contract processing, difficulties in hiring and training research personnel, lengthy process for shipment of reagents and equipment, and restricted funding availability may all negatively impact timely implementation of studies.

This recent experience highlights the urgent need to improve local preparedness for research in the setting of explosive outbreaks, as have been seen in the last few years in different countries. In fact, for infectious diseases with epidemic behavior, the best—and sometimes only—opportunity to test the efficacy of a new drug or vaccine among infected or at-risk human populations is during the outbreak itself.[12,13] Ebola and Zika epidemics are recent dramatic examples. In the case of Ebola treatment trials, despite expedited protocol development and ethical approval, additional barriers were faced over local staff deploying, legal contract processing, and coordination of different coexisting protocols.[14] Such limitations result in waste of financial and structural resources and lost research opportunities.[12]

URGENT ACTION POINTS FOR PREPAREDNESS

A list of points of delay faced during the development of our study along with specific suggestions for improvement is presented in Table 1. Further recommendations from expert panels and stakeholders have been recently published. They include the development of template documents and checklists for proposed protocols in emergency or epidemic situations[15]; elaboration of guidelines for research ethics review and training programs for healthcare staff, tailored for the sociocultural peculiarities in each setting[12]; coordination between ethics committees, stakeholders, and other oversight authorities for ensuring communication and efficient outbreak response[16]; and anticipated inclusion of the interests of pregnant women in the development of prevention and treatment interventions in the context of infectious disease outbreaks.[17]

TABLE 1
Points of delay in YF research conducted in Sao Paulo, January 2018, and potential strategies for improvement

Points of delay in YF research	Suggested strategies for improvement
Delays in knowledge transfer, including lengthy process for publication of scientific findings	Important research findings, especially those concerning diseases with high public health impact and those evaluating new medical interventions, should be made publicly available promptly, through traditional scientific journals or other platforms. Knowledge and use of existing non–peer-reviewed platforms such as bioRxiv[12] should be amplified in the scientific community, keeping in consideration the intrinsic limitations of non–peer-reviewed publications.
Predominance of empirical care provision approach over evidence-based decision in health care	Improvements in medical training on the importance of safety and efficacy studies for each new drug, device, or procedure are needed. Local regulations on emergency use of investigational drugs should be easily accessible and applied.
Lack of funds tailored for rapid allocation to emerging diseases with public health impact	Sponsors and funding agencies should create special funds, allowing for flexible and rapid allocation for urgent research purposes.
Delays in regulatory approval	International regulations on clinical research should include timeframe as a key element of regulatory procedures, prioritizing outbreaks that require quick scientific responses. In addition, local stakeholders and research institutions should accommodate the needs of emergency responses by fast-tracking contracts and financial operations.
Delays for importation of reagents and equipment	Delays in the shipping of reagents and other obstructions that delay customs clearance should be avoided through the existence of unambiguous regulations for accelerating transport and delivery of essential materials, not limited to research context, but also extending to public health response purposes.
Lack of trained human resources	Human resources and training in resource-limited settings should be improved to allow for local planning and development of well-designed protocols in anticipation of outbreaks that impact public health.

YF = yellow fever.

In conclusion, our experience with the YF outbreak in the State of Sao Paulo, Brazil, highlights the need for changes in research preparedness that are particularly critical in middle- and low-resource settings. Initiatives to improve the efficiency and quality of research response during public health emergencies and outbreaks should be implemented before their outburst. Stakeholders and international neutral bodies have a leading role in setting research priorities and strategies before it is too late.

Received July 26, 2019. Accepted for publication February 17, 2020.

Published online March 30, 2020.

Acknowledgments: We thank T. A.-S. and Shafferman for English revision.

Financial support: The present study was partially funded by the São Paulo Research Foundation (FAPESP; grant no 2016/01735-2).

Authors' addresses: Vivian I. Avelino-Silva, Luciana V. B. Casadio, Ana C. S. S. Nastri, and Izabel Marcilio, Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil, E-mails: viviansilva87@gmail.com, luciana.vilasboas@gmail.com, ana.catharina@hc.fm.usp.br, and izabel.marcilio@hc.fm.usp.br. Claudia Figueiredo-Mello, Instituto de Infectologia Emílio Ribas, Faculdade de Medicina da Universidade de Sao Paulo, São Paulo, Brazil, E-mail: claudiamello@ymail.com. Ana Freitas Ribeiro, Instituto de Infectologia Emílio Ribas, São Paulo, Brazil, E-mail: anafribeiro@uol.com.br. Anna S. Levin, Instituto de Medicina Tropical, Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil, E-mail: anna@usp.br. Ester C. Sabino, Instituto de Medicina Tropical, Sao Paulo, Brazil, E-mail: sabinoec@usp.br.

REFERENCES

1. Possas C, Martins RM, Oliveira RL, Homma A, 2018. Urgent call for action: avoiding spread and re-urbanisation of yellow fever in Brazil. *Mem Inst Oswaldo Cruz 113:* 1–2.
2. Rossetto EV, Angerami RN, Luna EJA, 2017. What to expect from the 2017 yellow fever outbreak in Brazil? *Rev Inst Med Trop Sao Paulo 59:* e17.
3. Couto-Lima D et al., 2017. Potential risk of re-emergence of urban transmission of yellow fever virus in Brazil facilitated by competent *Aedes* populations. *Sci Rep 7:* 4848.
4. Governo do Estado de São Paulo, Secretaria de Estado da Saúde, 2018. *Boletim Epidemiológico Febre Amarela - 30/04/2018*. Available at: http://www.saude.sp.gov.br/resources/cve-centro-de-vigilancia-epidemiologica/areas-de-vigilancia/doencas-de-transmissao-por-vetores-e-zoonoses/doc/famarela/fa18_boletim_epid_3004.pdf. Accessed August 22, 2018.
5. Monath TP, Vasconcelos PF, 2015. Yellow fever. *J Clin Virol 64:* 160–173.
6. Larsen FS et al., 2016. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. *J Hepatol 64:* 69–78.
7. Lee WM et al., 2009. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology 137:* 856–864.e1.
8. Duarte-Neto AN et al., 2019. Yellow fever and orthotopic liver transplantation: new insights from the autopsy room for an old but re-emerging disease. *Histopathology 75:* 638–648.
9. Bhatia HK, Singh H, Grewal N, Natt NK, 2014. Sofosbuvir: a novel treatment option for chronic hepatitis C infection. *J Pharmacol Pharmacother 5:* 278–284.
10. Freitas C, Higa L, Sacramento C, Ferreira A, Reis P, Delvecchio R, 2018. Yellow fever virus is susceptible to sofosbuvir both in vitro and in vivo. *bioRxiv 266361*. Available at: https://doi.org/10.1101/266361.
11. de Freitas CS et al., 2019. Yellow fever virus is susceptible to sofosbuvir both in vitro and in vivo. *PLoS Negl Trop Dis 13:* e0007072.
12. Bain LE, Ngwain CG, Nwobegahay J, Sumboh JG, Nditanchou R, Awah PK, 2018. Research ethics committees (RECs) and epidemic response in low and middle income countries. *Pan Afr Med J 31:* 209.
13. Keusch GT, McAdam K, 2017. Clinical trials during epidemics. *Lancet 389:* 2455–2457.
14. Lang T, 2015. Ebola: embed research in outbreak response. *Nature 524:* 29–31.
15. Aarons D, 2018. Research in epidemic and emergency situations: a model for collaboration and expediting ethics review in two Caribbean countries. *Dev World Bioeth 18:* 375–384.
16. Saxena A et al., 2019. Ethics preparedness: facilitating ethics review during outbreaks - recommendations from an expert panel. *BMC Med Ethics 20:* 29.
17. Krubiner CB et al., 2019. Pregnant women and vaccines against emerging epidemic threats: ethics guidance for preparedness, research, and response. *Vaccine*. [Epub ahead of print May 3, 2019]. pii: S0264-410X(19)30045-3. Available at: https://doi.org/10.1016/j.vaccine.2019.01.011.