

8. *Tocilizumab Improves Significantly Clinical Outcomes of Patients with Moderate or Severe COVID-19 Pneumonia*. Available at: <https://www.aphp.fr/contenu/tocilizumab-improves-significantly-clinicaloutcomes-patients-moderate-or-severe-covid-19>. Accessed April 27, 2020.
9. Gritti, G., Raimondi, F., Bottazzi, B et al. Siltuximab downregulates interleukin-8 and pentraxin 3 to improve ventilatory status and survival in severe COVID-19. *Leukemia*. 2021. doi: 10.1038/s41375-021-01299-x.
10. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19. *New Engl J Med*. 2020;383:2333–2344.
11. Hermine O, Mariette X, Tharaux PL, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med*. 2020;12.
12. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA Intern Med*. 2021;181:24–31.
13. Talluri, K., Lall, N., Moreno, M.A., Nichols, L. and Bande, D., 2021. Posterior Reversible Encephalopathy Syndrome in a Patient With SARS-CoV-2 Infection Treated With Tocilizumab. *Cureus*. 2021;13. doi: 10.7759/cureus.13475.
14. Rosa Junior M, Borges EI, Fonseca APA, et al. Posterior reversible encephalopathy syndrome during treatment with tocilizumab in juvenile idiopathic arthritis. *Arq Neuropsiquiatr*. 2018;76:720–721.
15. Kushner BH, Modak S, Basu EM, et al. Posterior reversible encephalopathy syndrome in neuroblastoma patients receiving anti-GD2 3F8 monoclonal antibody. *Cancer*. 2013;119:2789–2795.

Inaccurate Real-World Data Does Not Provide Real-World Answers

To the Editor:

We would like to congratulate Kory et al¹ for their article. From the beginning of the COVID-19 pandemic, there emerged the need to find a drug that could alter the course of severe infection and reduce mortality, was easily accessible, and was inexpensive. Ivermectin, among others, is a potential drug with these properties.

Numerous studies on the subject, of variable quality, have been published, but evidence of the effectiveness of ivermectin is inconclusive. The review article by Kory et al attempted to consolidate the existing evidence on ivermectin to justify its recommendation.

The authors used real-world data from 3 South American countries, Brazil, Paraguay, and Peru.

A more detailed and in-depth analysis of these data shows us that they do not provide enough evidence of effectiveness of ivermectin because there are discrepancies from the official data and the previous use of lockdown and other preventive public health measures was not adequately considered.

Data from Brazil published in the article differ from the official data.² As shown in Table 1, the number of cases of COVID-19 did not decrease after the introduction of ivermectin, as shown by the authors of the

Table 1. Comparison of number of COVID-19 cases in Brazilian cities with and without Ivermectin distribution campaigns.

	June	July	August	Change from June to August (%)
Itajaí	1385 (2123)	1891 (2854)	2733 (998)	97% (–53%)
Chapecó	1583 (1760)	1337 (1754)	1926 (1405)	22% (–20%)
Macapá	7960 (7966)	2501 (2481)	1742 (2370)	–78% (–70%)
Ananindeua	1620 (1520)	1523 (1521)	991 (1014)	–39% (–30%)
Natal	8695 (9009)	7497 (7554)	3304 (1590)	–62% (–82%)
João Pessoa	9939 (9437)	8032 (7963)	5555 (5384)	–41% (–43%)

Source: Brazilian Health Ministry- <https://covid.saude.gov.br/>.

The cities shown in bold distributed ivermectin; the neighboring regional cities below did not. Percent difference (% difference between June and August). The number of cases published in Kory's article is shown in parentheses.

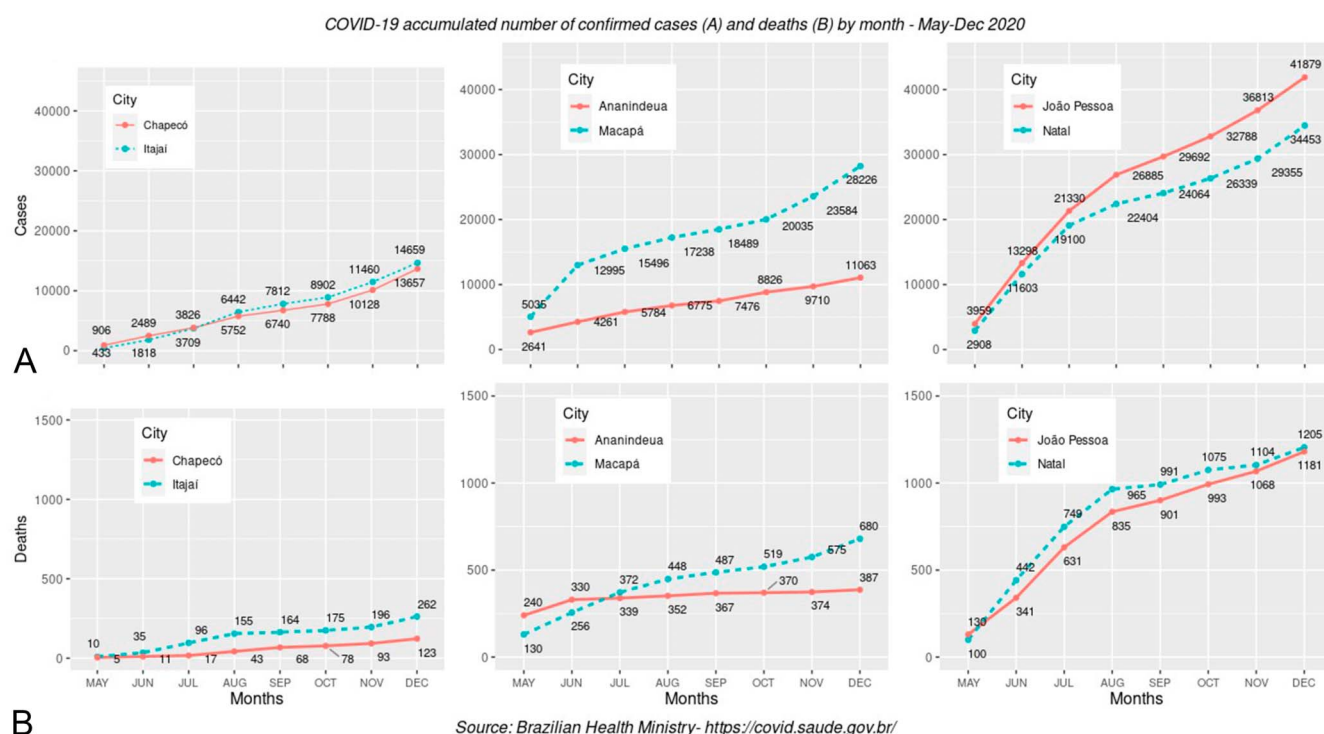


FIGURE 1. COVID-19 notifications in Brazilian cities, May–December 2020. Cumulative number of confirmed cases (A) and deaths (B). The cities where ivermectin was widely used are shown in blue.

article for Itajai city. On the contrary, the number of cases rapidly increased.

Some Brazilian cities (such as Macapá and Itajai) where ivermectin was widely used became the cities with the highest case fatality rate at the beginning of 2021, while Ivermectin continued to be administered to the population.^{3,4}

We also analyzed the number of cases and deaths for the 6 Brazilian cities cited in the article between May and December 2020. As shown in Figure 1, there is no evidence that ivermectin was effective despite its extensive use.

Another epidemiological argument in the article, for ivermectin effectiveness, was the decrease in the number of cases in the state of Alto Paraná in Paraguay. According to data obtained from the Pan American Health Organization, the number of COVID-19 cases in the state of Alto Paraná began to decrease 3 weeks before the administration of ivermectin was introduced.⁵ In fact, lockdown measures were adopted by the Paraguayan health authorities between July 29, 2020, and October 5, 2020.

As any ivermectin protective effect cannot begin before its administration as in Paraguay and when a series of measures are taken together, including ivermectin, the success in cases diminution cannot be attributed to just one of the components of the plan, as the authors suggested.

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Regarding the evidence from Peru, the use of ivermectin was not dissociated from other health measures. The Peruvian government developed the Tayta plan to deal with COVID-19. The Tayta plan included not only the use of ivermectin but also basic care measures, such as oxygen supply and preventive measures such as testing, case detection, and case isolation. Therefore, the changes in the incidence rates cannot be attributed exclusively to the use of ivermectin.^{6,7}

Therefore, all 3 country examples cited as epidemiological evidence of ivermectin effectiveness presented either show considerable discrepancy from the official data or the effects attributed to ivermectin depend on temporal associations that coincided with multiple preventive measures being implemented and not to ivermectin administration per se.

Considering all the above arguments, and the complexity of this pandemic, we believe that only large-scale randomized controlled trials can determine the utility, if any, of the administration of ivermectin.

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American Journal of Therapeutics (2021) 28(5)

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The code used for the figures is available at https://github.com/mbuffet808/Covid-19_Study_Brazil.

The authors have no conflicts of interest to declare.

REFERENCES

1. Kory P, Meduri GU, Varon J, et al. Review of the emerging evidence demonstrating the efficacy of ivermectin in the prophylaxis and treatment of COVID-19. *Am J Ther.* 2021;28:e299.
2. Brazilian Ministry of Health. *Painel de casos de doença pelo coronavírus 2019 (COVID-19) no Brasil pelo Ministério da Saúde. [database online].* 2021. Available at: <https://covid.saude.gov.br/>. Accessed at May 15, 2021.
3. Mattei L. *Boletim COVID-19 EM SC N.39—06.02.2021.* Available at: <https://noticias.paginas.ufsc.br/files/2021/02/060221Boletim-N39.pdf>. Accessed May 22, 2021.
4. *Boletim Epidemiológico N. 4 COVID-19.* Available at: https://editor.amapa.gov.br/arquivos_portais/publicacoes/SVS_b24dbacc613c6fa0cdddee394e2ea118.pdf. Accessed May 22, 2021.
5. PAHO. *Informe de situación COVID-19 OPS/OMS Paraguay, n.25 (11 de septiembre del 2020).* Available at: <https://iris.paho.org/handle/10665.2/53035>. Accessed May 19, 2021.
6. Peruvian Ministry of Health. *Resolución Ministerial 270-2020-MINSA.* Available at: <https://www.gob.pe/institucion/minsa/normas-legales/563764-270-2020-minsa>. Accessed May 19, 2021.
7. Peruvian Government. *Control en la pandemia por la COVID-19.* Available at: <https://www.gob.pe/institucion/contraloria/informes-publicaciones/1891695-control-en-la-pandemia-por-la-covid-19>. Accessed May 19, 2021.

Lisinopril-Associated Recurrent Hemorrhagic Pancreatitis

To the Editor:

Acute pancreatitis is a leading cause of hospitalization in the United States. It can lead to significant morbidity and mortality, usually because of systemic inflammatory response syndrome leading to organ failure, sepsis, and related complications.¹ The overall mortality of acute pancreatitis is approximately 5%, although it could be as high as 17% in necrotizing pancreatitis. The differential diagnoses of underlying etiologies causing pancreatitis is broad with medications being a rare cause.⁶ Here, we present a case of recurrent hemorrhagic pancreatitis from use of lisinopril.

A 52-year old Caucasian man with a history of type-2 diabetes and hypertension presented to the emergency department with generalized abdominal pain which radiated upward into his chest, giving him a sharp pain and a feeling of constant tightness that awoke him from sleep the night before. No alleviating or exacerbating factors. He denied fever, nausea, vomiting, constipation, diarrhea, chest pain, and shortness of breath. He has a history of alcohol use although he quit 6 years before admission. He has a history of gallstones and had laparoscopic cholecystectomy several years before admission. He reported a prior episode of pancreatitis 12 years ago. His medications include

lisinopril and metformin. On physical examination, blood pressure was 177/89 mm Hg, pulse 97/min, temperature of 97.1°F. Patient was awake and alert, but looked uncomfortable. Physical exam was significant for diffuse abdominal tenderness with voluntary guarding, and no rebound tenderness. Lab work up was notable for white blood cell count of 12.7 per microliter (neutrophils 87.6%), hemoglobin 17 g/dL, platelets 195×10^9 per liter, creatinine 1.2 mg/dL, potassium 5.4 mmol/dL, CO₂ 22 mmol/dL, lipase 1049 IU/L, and triglyceride 314 mg/dL. Computed tomographic angiography (CT) of the abdomen and pelvis demonstrated moderate peripancreatic (body/tail region) stranding with relative diminished enhancement of these portions of the pancreas consistent with pancreatitis. Mild mucosal thickening of the proximal aspect of the descending colonic segment was also noted. He was treated with intravenous fluids and pain medications. He did not receive any antibiotic. He improved clinically and was discharged after 3 days to follow-up with primary care. The cause of pancreatitis is believed to be idiopathic.

He was readmitted 2 months later with a similar clinical presentation. He reported epigastric radiation to his lower abdomen, more on the right side, worse than last episode. He was hypotensive (blood pressure