

Lessons for the coronavirus (COVID-19) “not safe at any speed” thinking for the United States Food and Drug Administration (FDA) still applies

Charles Bennett^{1*}, MD., PhD., MPP., and Linda Martin¹, PhD.

¹Department of Clinical Pharmacology and Outcomes Sciences, College of Pharmacy, University of South Carolina, Columbia, SC 29208 USA

There has been extensive news coverage about the USA Food and Drug Administration’s (FDA’s) role in approving medications to treat the coronavirus (COVID-19) and vaccines to prevent the virus while at the same time, ensuring medication safety. COVID-19 treatment was initially focused on hydroxychloroquine and now has changed to remdesivir. Coronavirus vaccination development is now a competitive and collaborative 14-industry program that USA President Donald Trump has named “Operation Warp Speed”. With the goals of having FDA approved treatments in the clinic as soon as possible and vaccines in mass production by the end of the year, safety is likely to be overlooked—again.

In the 1965 classic book “Unsafe at any Speed”, Ralph Nader describes automobile engineers as being so focused on production and getting automobiles to market that there is a general disregard for safety. This concern about speed at the expense of safety continues today. Vaccines which will be given to hundreds of millions of people and antiviral medications which will be administered to thousands of people are public health emergencies that demand attention to safety, as well as efficacy.

Is safety likely to be considered within “Operation Warp Speed?” Are the 14 companies competing to develop coronavirus vaccines collaborating on safety while they furiously race to make the first vaccine? Current therapeutic approaches to COVID-19 vaccines and therapies raise doubt that public health safety will be given its due.

Although not widely discussed, fluoroquinolone (FQ) antibiotics are currently part of a therapeutic regime currently being used to treat some COVID-19 patients. As such, FQ antibiotics provide a timely example of public safety taking a back seat.

FQ antibiotics, such as cipro/ciprofloxacin, levaquin/levofloxacin, and avelox/moxifloxacin, are now being administered to some coronavirus patients. The March 1, 2020 study in *The Lancet*, “Therapeutic and triage strategies for 2019 novel coronavirus disease in fever clinics,” by

Zhang, et al., outlines the recommended use of moxifloxacin for coronavirus patients [1]. Additionally, a February 7, 2020 study from the *Journal of American Medicine Network*, “Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China” explains that 64.4% of the COVID-19 patients in the study received the FQ moxifloxacin [2].

Although hundreds of millions of FQ antibiotic prescriptions have been written annually for more than three decades, Charles Bennett, MD., PhD., MPP., SmartState Chair, Director of the Center for Medication Safety and Efficacy at the University of South Carolina, and Director of the Southern Network on Adverse Reactions (SONAR), has raised concerns over FQ safety for nearly a decade. Dr. Bennett initiated his SONAR investigation of FQs in response to concerns raised by Linda Martin, PhD. Dr. Martin has experienced severe, widespread, disabling FQ adverse events for years following levaquin use.

While the FDA has been slow to act regarding FQ safety concerns, thanks to a unique collaboration between patients suffering from FQ toxicity, referred to as having been “floxed,” and Dr. Bennett, attention has been drawn to the dangers of these antibiotics which are approved by the FDA to treat both serious infections, such as anthrax and the plague, and routine infections, such as sinus infections

***Corresponding author:** Charles Bennett, M.D., Ph.D., M.P.P., Department of Clinical Pharmacology and Outcomes Sciences, College of Pharmacy, University of South Carolina, Columbia, SC 29208 USA. Email: bennettc@cop.sc.edu

Received 11 May 2020 Accepted 26 May 2020 Published 1 June 2020

Citation: Bennett C, Martin L. Lessons for the coronavirus (COVID-19) “not safe at any speed” thinking for the United States Food and Drug Administration (FDA) still applies. J Cancer Res Ther. 2020; 8(3):17-20. DOI: [10.14312/2052-4994.2020-3](https://doi.org/10.14312/2052-4994.2020-3)

Copyright: © 2020 Bennett C, et al. Published by NobleResearch Publishers. This is an open-access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

and urinary tract infections. As documented in the FDA's Adverse Events Reporting System (FAERS), patients have experienced an estimated 3 million plus adverse events over the years associated with FQs—accounting for one of the top three drug classes associated with adverse events in FAERS.

Raising awareness of common, but overlooked, FQ adverse events are now more important than ever, given that FQs remain first line therapies for many physicians for treating pneumonia, a complication of the coronavirus. Given that FQs are being recommended for use in some COVID-19 patients, physicians prescribing FQs and patients consuming FQs for the coronavirus should be aware of FQ public health and drug safety concerns.

The following are key actions taken by Drs. Bennett and Martin to raise awareness about the dangers of FQs, as well as, unacceptably slow responses from the FDA:

- After being floxed by Johnson & Johnson's FQ levaquin in 2011, Linda Martin discovered that a number of levaquin clinical trials were considered by the clinical trial reviewers to have "significant flaws". Some aspects were described as "confusing" or "troubling". Some of the trials were considered to have "significant flaws in the protocol design" and "significant flaws in protocol implementation" while some were considered to have clinical assessment categories which were "inappropriate". A clinical trial reviewer considered one levaquin clinical trial to be "quite confusing from the clinical microbiology perspective" and said it contained "troubling" variations. In addition, it was noted that "some of the proposed quality control parameters simply do not make sense". The FDA approved levaquin anyway.
- Since 2014, Drs. Bennett and Martin have communicated with reporters from across the country on more than 50 local news stories exposing the dangers of FQ antibiotics. These stories featured interviews with local residents who suffer from FQ toxicity. An FQ story from Atlanta by Jim Strickland received a Regional Emmy Award in 2014 and a second FQ story from Cleveland's Ron Regan also received a Regional Emmy award.
- In August 2014, Dr. Martin submitted comments for a September 23, 2014 FDA Advisory Committee which would discuss the use of levaquin in children. Based on FDA briefing materials for this meeting, approximately 100,000 children had already been prescribed levaquin even though the FDA has only approved levaquin for children to treat anthrax and the plague. Dr. Martin requested that the FDA reconsider allowing levaquin to be used off-label for children based on the FDA's own FQ adverse events data.
- In September 2014, Drs. Bennett and Martin submitted a Citizen Petition to the FDA requesting that more warnings of psychiatric adverse events be added to the levaquin label. The petition also asked the FDA to add a specific "Psychiatric effects" heading on the levaquin label which would include the following adverse events: toxic psychoses, restlessness, anxiety, confusion, hallucinations, paranoia, depression, nightmares, insomnia, suicidal thoughts or acts, feeling abnormal, loss of consciousness, disorientation, agitation, delirium, depressed level of consciousness, amnesia, coma, disturbance in attention, panic attack, memory impairment, and nervousness, noting that these events may start during treatment or may be delayed and start days, weeks, or months after the last dose. Finally, the petition requested that the FDA add psychiatric adverse events, including suicide, to the "Levaquin Black Box", the most serious type of warning.
- In November 2014, Drs. Bennett and Martin met with staff from the U.S. Senate Health Committee, asking for the committee's assistance in asking the FDA to add more safety warnings to FQ labels.
- In August 2015, Drs. Bennett and Martin and other floxed individuals participated in a meeting with FDA staff regarding FQ adverse events and FQ safety concerns.
- On November 5, 2015, Dr. Bennett attended the FDA Joint Advisory Committee for Antibiotics and Drug Safety in Maryland and discussed FQ safety issues. At this meeting, FDA Epidemiologist Debra Boxwell, Ph.D. described the constellation of FQ adverse events as "Fluoroquinolone-Associated Disability (FQAD)" and defined it as disability which results in a "substantial disruption of a person's ability to conduct normal life functions" and having "adverse events reported from two or more of the following body systems: musculoskeletal, neuropsychiatric, peripheral nervous system, senses (vision, hearing, etc.), skin, cardiovascular". Dr. Boxwell further indicated that in order to meet this FQAD definition, these adverse events must "last 30 days or longer after stopping the fluoroquinolone".
- In February 2016, SONAR and Drs. Bennett and Martin collaboratively published "Fluoroquinolone-related neuropsychiatric and mitochondrial toxicity: a collaborative investigation by scientists and members of a social network", by Kaur, et. al. [3]. This study documents that "mice treated with ciprofloxacin had lower grip strengths, reduced balance, and depressive behavior compared with the controls". Additionally, this study describes that a survey of floxed individuals indicated that "93 of 94 respondents reported FQ-associated events including anxiety, depression, insomnia, panic attacks, clouded thinking, depersonalization, suicidal thoughts, psychosis, nightmares, and impaired memory beginning within days of FQ initiation or days to months of FQ discontinuation". Furthermore, this study concludes that "levofloxacin and ciprofloxacin toxicities were neurologic (30% and 26%, respectively), tendon damage (8% and 6%), and psychiatric (10% and 2%)".

On July 26, 2016, almost nine months after the November 2015 Advisory Committee meeting, the FDA requested that FQ manufacturers update the FQ product labels to disclose that FQs "have been associated with disabling

and potentially irreversible serious adverse reactions that have occurred together, including: tendinitis and tendon rupture, peripheral neuropathy, central nervous system effects." The FDA, however, failed to require FQ makers to warn of FQAD, as defined by FDA epidemiologist Dr. Boxwell, almost nine months earlier.

- In March 2018, Dr. Bennett and the collaborative work with Dr. Martin, SONAR, and Andrew Bennett, an undergraduate at the University of South Carolina, were featured in a three-page *Nature* article, "When antibiotics turn toxic", by Jo Marchant [4]. In this article, Dr. Bennett explains that "prior work [from his National Institutes of Health funded research found that only 1% of serious adverse events associated with four commonly used drugs] were reported to the FDA, suggesting that fluoroquinolones might have harmed hundreds of thousands of people in the United States alone". The *Nature* article also discusses findings reported by Andrew Bennett at a national oncology meeting regarding a gene identified that appears to be associated with increased risk for ciprofloxacin-associated neuropsychiatric toxicity.

It was not until July 2018, almost four years after Drs. Bennett and Martin submitted the Citizen Petition to the FDA, that the FDA approved the requests to require FQ manufacturers add additional psychiatric adverse events to the levaquin label and to create a separate label subheading for psychiatric adverse events. This change would mean that often devastating psychiatric effects would no longer be meshed under the general central nervous system heading. Additionally, the FDA acknowledged that psychiatric adverse events, including suicide, were assumed to already be included in the "Levaquin Black Box" warning, as part of central nervous system events. Unfortunately, the FDA failed to acknowledge that most physicians and patients will not assume that central nervous system events include psychiatric side effects, including suicide. Because fluoroquinolones have class effect, these label changes were applied to all FQs.

- Because suicide is such a significant, under-recognized FQ adverse event, in September 2018 SONAR, Drs. Bennett and Martin and the SONAR team collaboratively reported "Fluoroquinolone-associated suicide", by Kommalapati, et. al. [5]. This study describes that "several case reports have raised concerns that exposure to fluoroquinolones (FQs) may increase the risk of suicidal behavior". This study explains that "of the 122 FQ-associated suicide or suicide-attempt events reported to the FDA, 108 met inclusion criteria" for the study and "half of the events described completed suicides". It further describes that "40% of the events occurred within two weeks of FQ initiation". Finally, this study "highlights the importance of continued awareness of fluoroquinolone-associated suicide-related events, which can occur even in patients without prior psychiatric illness".
- The 201 Pharmaceutical Risk Advisory Committee of the European Medicines Agency (EMA)- met in 2018

and asked for and received my written testimony as well as heard from FQ-affected persons from 13 countries. My written testimony is in the final record and several patients referred to it in their record. The Pharmacovigilance Risk Assessment Committee (PRAC) recommended that FQs not be first line antibiotics. The Committee for Health and Medical Products agreed (CHMP) and this become regulation in all then 28 EU countries.

- In October 2019, Drs. Bennett and Martin submitted another Citizen Petition 2019-P-2998 [6] to the FDA, this time asking for warnings of FQAD to be added to the levaquin label, asking for psychiatric adverse events to be specifically identified in the "Black Box" warnings, and asking for a levaquin Risk Evaluation and Mitigation strategy (REMS) which would require patients to give written consent prior to taking levaquin.
- In November 2019, SONAR, Andrew Bennett, and Drs. Bennett and Martin published "An evaluation of reports of ciprofloxacin, levofloxacin, and moxifloxacin-association neuropsychiatric toxicities, long-term disability, and aortic aneurysms/dissections disseminated by the FDA and the EMA" [7]. This study notes that the FDA and the European Medicines Agency (EMA) "report that neuropsychiatric toxicity, long-term disability, and aortic dissections/aneurysms occur with all FQs. Disability and neuropsychiatric toxicity can occur after one dose or several months after FQs. United States' and European' regulators warn physicians not to prescribe FQs for uncomplicated acute urinary tract infection, sinusitis, or bronchitis, unless other possible choices are tried first, as risks outweigh benefits in these settings".

To date, the FDA has failed to act on the most recent Citizen Petition submitted by Drs. Bennett and Martin.

As defined in Chapter 9 of the Federal Food, Drug and Cosmetics Act, the FDA shall "protect the public health" by ensuring that human "drugs are safe". Now is the time for the FDA to take action to require FQ manufacturers to add FQAD to the FQ labels; to specifically identify psychiatric adverse events, including suicide, in FQ "Black Box" warnings; and to implement an FQ REMS, especially given that some COVID-19 patients are consuming these antibiotics without the additional warnings.

Too many people have needlessly died or have been needlessly, severely disabled following use of FQs—without adequate safety warnings. The FDA has failed to adequately warn physicians and patients about the dangers of these commonly prescribed antibiotics which are currently being prescribed for some COVID-19 patients.

The FDA should act now to adequately warn physicians and patients about the dangers of FQ antibiotics. For more than a decade, Drs. Bennett and Martin, and others have worked tirelessly to disclose serious, disabling, often permanent FQ adverse events. Now it is time for the FDA to act.

The FDA's lack of adequate, timely attention to FQ safety concerns provides important lessons directly applicable to "Operation Warp Speed". This is a clear analogy to Ralph Nader's "Unsafe at any Speed" and the automotive industry.

Forewarned is forearmed!

Conflicts of interest

Authors declare no conflicts of interest.

References

- [1] Zhang J, Zhou L, Yang Y, Peng W, Wang W, et al. Therapeutic and triage strategies for 2019 novel coronavirus disease in fever clinics. *Lancet Respir Med.* 2020; 8(3):e11–e12.
- [2] Wang D, Hu B, Hu C, Zhu F, Liu X, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* 2020; 323(11):1061–1069.
- [3] Fluoroquinolone-related neuropsychiatric and mitochondrial toxicity: A collaborative investigation by scientists and members of a social network. *J Community Support Oncol.* 2016; 14(2):54–65.
- [4] Marchant J. When antibiotics turn toxic. *Nature.* 2018; 555(7697):431–433.
- [5] Kommalapati A, Wallam S, Tella SH, Qureshi ZP, Bennett CL. Fluoroquinolone-associated suicide. *Eur J Intern Med.* 2018; 55:e21–e22.
- [6] <https://www.regulations.gov/docketBrowser?rpp=25&so=DESC&sb=commentDueDate&po=0&D=FDA-2019-P-2998>
- [7] Bennett AC, Bennett CL, Witherspoon BJ, Knopf KB. An evaluation of reports of ciprofloxacin, levofloxacin, and moxifloxacin-association neuropsychiatric toxicities, long-term disability, and aortic aneurysms/dissections disseminated by the Food and Drug Administration and the European Medicines Agency. *Expert Opin Drug Saf.* 2019; 18(11):1055–1063.