



U.S. OFFICE OF SPECIAL COUNSEL

1730 M Street, N.W., Suite 300
Washington, D.C. 20036-4505

The Special Counsel

September 27, 2016

The President
The White House
Washington, D.C. 20500

Re: OSC File No. DI-16-3709

Dear Mr. President:

Pursuant to my responsibilities as Special Counsel, I am forwarding a report from the U.S. Department of Health and Human Services (HHS) in response to Dr. Robert S. Lanciotti's¹ disclosures of wrongdoing at the Centers for Disease Control and Prevention (CDC), Emergency Operations Center (EOC).² Dr. Lanciotti joined the CDC's Vector-Borne Diseases Division as a microbiologist in 1989 and has served as Chief of the Diagnostics and Reference Laboratory Activity, Arbovirus Diseases Branch, in Fort Collins, Colorado, since 2000. In this capacity, Dr. Lanciotti is responsible for developing assays (tests) to identify and diagnose viral diseases transmitted by mosquitos, ticks, and fleas, including dengue, chikungunya, West Nile Virus, and Zika. Dr. Lanciotti disclosed that EOC scientists recommended that state and territory public health department laboratories (public health laboratories) use the Trioplex Real-time RT-PCR Assay (Trioplex) for Zika Virus Disease (Zika) diagnostic testing, despite information indicating that it is less analytically sensitive in detecting Zika virus ribonucleic acid (RNA) than the Singleplex Real-time RT-PCR Assay (Singleplex). Dr. Lanciotti contended that use of the Trioplex in place of the Singleplex will result in an additional 39 percent of Zika infections in their acute phase going undetected.

I referred Dr. Lanciotti's allegations to the Honorable Sylvia Mathews Burwell, Secretary, HHS, for investigation pursuant to 5 U.S.C. § 1213(c) and (d).³ Secretary

¹ Dr. Lanciotti consented to the Office of Special Counsel's (OSC) public release of his name.

² The EOC is the CDC's command center for monitoring and coordinating the emergency response to the Zika virus, bringing together CDC scientists with expertise in arboviruses like Zika, reproductive health, birth defects, developmental disabilities, and travel health. The EOC was activated for Zika on January 22, 2016 and moved to Level 1 activation—the highest level—on February 8, 2016. The EOC's work includes, among other things, developing laboratory tests to diagnose Zika, conducting studies to learn more about the link between Zika and microcephaly, and monitoring and reporting cases of Zika to help the CDC better understand how and where Zika is spreading. See: <http://www.cdc.gov/zika/cdc-role.html>.

³ OSC is authorized by law to receive disclosures of information from federal employees alleging violations of law, rule, or regulation, gross mismanagement, a gross waste of funds, an abuse of authority, or a

The President
September 27, 2016
Page 2 of 5

Burwell directed Dr. Steve Monroe, Associate Director for Laboratory Science and Safety, CDC, to conduct the agency investigation. Secretary Burwell submitted a written report detailing the agency's findings to the Office of Special Counsel (OSC) within the requisite 60 days. In accordance with 5 U.S.C. § 1213(e), the following is a summary of the investigation, Dr. Lanciotti's response, and my findings.

Dr. Lanciotti's Allegations

Dr. Lanciotti alleged that use of the Trioplex in place of the Singleplex in a clinical setting would result in an additional 39 percent of Zika infections in their acute phase going undetected. Dr. Lanciotti reached this conclusion following his analysis of the results of a multi-assay comparative study performed in his laboratory, as well as summary data compiled by the Blood Systems Research Institute (BSRI), an independent research institution external to the CDC. Dr. Lanciotti provided data evidencing the Trioplex's decreased analytical sensitivity relative to the Singleplex to EOC scientists in April 2016, but the EOC continued to recommend that public health laboratories run the Trioplex. Finally, Dr. Lanciotti alleged that EOC scientists' promotion of the Trioplex may have led public health laboratories that were approved to use the Singleplex to run the Trioplex preferentially, based on the incorrect belief that it is the superior method for detecting Zika virus RNA.

The Agency Investigation

The agency investigation did not substantiate Dr. Lanciotti's allegations, finding that "[t]here is insufficient, statistically robust, definitive data to reach an evidence-based conclusion that use of the Trioplex assay over the Singleplex in clinical practice will result in 39 percent of Zika virus infections being missed." The agency concluded that while EOC scientists did not relay Dr. Lanciotti's concerns regarding the Trioplex's decreased analytical sensitivity relative to the Singleplex to public health laboratories and continued to recommend the Trioplex, this did not mean that they knowingly promoted an inferior assay. The agency acknowledged that the EOC's promotion of the Trioplex may have led some public health laboratories to run the Trioplex over the Singleplex. However, given the absence of statistically significant data demonstrating that the Trioplex is less analytically sensitive than the Singleplex, the agency determined that this

substantial and specific danger to public health and safety. 5 U.S.C. § 1213(a) and (b). OSC does not have the authority to investigate a whistleblower's disclosure; rather, if the Special Counsel determines that there is a substantial likelihood that one of the aforementioned conditions exists, she is required to advise the appropriate agency head of her determination, and the agency head is required to conduct an investigation of the allegations and submit a written report. 5 U.S.C. § 1213(c). Upon receipt, the Special Counsel reviews the agency report to determine whether it contains all of the information required by statute and that the findings of the head of the agency appear to be reasonable. 5 U.S.C. § 1213(e)(2). The Special Counsel will determine that the agency's investigative findings and conclusions appear reasonable if they are credible, consistent, and complete based upon the facts in the disclosure, the agency report, and the comments offered by the whistleblower under 5 U.S.C. § 1213(e)(1).

The President
September 27, 2016
Page 3 of 5

was not improper. The agency explained that the Trioplex's ability to detect Zika, chikungunya, and all four dengue virus RNA using a single clinical sample is both efficient and has important clinical implications. Because Zika, dengue, and chikungunya viruses are circulated by the same species of mosquito and may present with similar symptoms in infected individuals, testing for all three viruses at the same time offers clinicians valuable information to distinguish the viruses and guide patient care. Finally, the agency noted that seven public health laboratories continue to use the Singleplex.

The investigative team acquired and analyzed data from comparative studies performed in the two laboratories led, respectively, by Dr. Lanciotti in Fort Collins, Colorado and Dr. Jorge Munoz, Chief, Diagnostics and Research Laboratory Activity, Dengue Branch, CDC, in San Juan, Puerto Rico, who developed the Trioplex. The investigative team also reviewed summary data derived from blind studies performed by multiple laboratories, including Dr. Lanciotti's and Dr. Munoz's laboratories, using their respective assays and methodologies on serum samples provided by the BSRI. The agency determined that the data derived from Dr. Lanciotti's comparative study could not serve as a basis for a valid comparison between the Trioplex and Singleplex because Dr. Lanciotti did not follow the Trioplex EUA protocol precisely. Specifically, Dr. Lanciotti used a different cycle threshold (Ct) cutoff value⁴—37.5 instead of 38.5—and different RNA extraction and amplification instrumentation than the protocol recommends.

The agency also rejected the BSRI's summary data, because Dr. Lanciotti used more serum in the Singleplex than Dr. Munoz did in the Trioplex. In other words, the data compiled by the BSRI compares the performance of a standard input volume Trioplex to that of a high input volume Singleplex. The agency acknowledged that the current Trioplex EUA authorizes only a standard input volume for the Trioplex, while the Singleplex is not subject to such a limitation. However, the agency stated that on August 22, 2016, the CDC submitted a substantial amendment to the Trioplex EUA for FDA approval. The amendment, if approved, will authorize the use of larger sample volumes in the assay. Additionally, the agency determined that the data derived from Dr. Munoz's comparative study, which show no difference in the analytical sensitivity of the Trioplex relative to the Singleplex, provide "the highest quality comparison" of the two assays because Dr. Munoz ran the Trioplex according to the EUA protocol and ran the Singleplex using the same RNA and extraction protocols as the Trioplex EUA. Finally, the agency asserted that Trioplex results—or results of any Real-Time RT-PCR assay—are not intended to be used as the sole basis for clinical diagnoses; rather, they are to be interpreted in conjunction with a review of the patient's history, clinical signs, and symptoms.

⁴ According to the agency report, the Ct cutoff value refers to the number of cycles of rapid heating and cooling that a serum sample runs through after which identification of the target deoxyribonucleic acid (DNA) sequence cannot be reliably obtained due to the degradation of fluorescent probes.

The President
September 27, 2016
Page 4 of 5

Dr. Lanciotti's Comments in Response to the Agency Report

In his comments, Dr. Lanciotti disagreed with the agency's findings. First, he noted that the agency report made no mention of the fact that CDC's Fort Collins laboratory—which has “the greatest experience in Zika virus testing”—continues to use the Singleplex due to concerns regarding the Trioplex's decreased analytical sensitivity. Dr. Lanciotti further explained that according to the data from his multi-assay comparative study, the Trioplex is “significantly less sensitive” than dengue singleplex assays in detecting the four dengue viruses, thus calling into question the agency's assertion that use of the Trioplex has important clinical implications because it provides for the detection of three related viruses.

Dr. Lanciotti also disagreed with the agency's assessment of the data derived from his multi-assay comparative study and the BSRI's summary data. He explained that the instrument used in his comparative study is a newer model of the recommended Trioplex EUA instrument and that it is well established that the use of different instruments for RNA extraction and amplification has no effect on the qualitative outcome of the assay. Dr. Lanciotti further rejected the agency's contention that his data could not serve as a basis for a valid comparison between the Trioplex and Singleplex because he used a different Ct cutoff value than the Trioplex EUA protocol recommends. He stated that he provided raw numerical data to EOC scientists so that they could apply whatever cutoff they chose. He stated that using the EUA recommended cutoff value of 38.5 actually raised the percentage of Zika infections in their acute phase going undetected to 40 percent.

Finally, Dr. Lanciotti dismissed the agency's concerns over the BSRI's summary data, stating that the BSRI study is “the most accurate method to evaluate the clinical sensitivity (how the test will perform under real world conditions) of individual assays.” He explained that the BSRI provided participating laboratories identical panels of blind-coded specimens to test using their own assays and methodologies. The BSRI then compiled and reviewed the data produced by the laboratories, and the Trioplex emerged as the least sensitive of all evaluated assays. Dr. Lanciotti acknowledged that the CDC's proposed amendment to the Trioplex EUA to allow for the use of larger sample volumes may increase the Trioplex's analytical sensitivity. However, he noted that studies have demonstrated that when primers directed against multiple pathogens are combined into a single assay—Zika, dengue, and chikungunya, in the case of the Trioplex—the sensitivity of the assay is inherently reduced. Dr. Lanciotti also cautioned that the Trioplex's inflexibility due to its detailed, precise EUA protocol is a “fatal flaw,” pointing to the fact that a single change in the Trioplex EUA protocol designed to address the sensitivity problem that he raised in April 2016 took until August 22, 2016 for the EOC to disseminate. Dr. Lanciotti asserted that “[t]he entire EOC concept as an approach to epidemic response by [the] CDC needs to be reevaluated” in light of the problems that have ensued following the EOC's recommendation of the Trioplex.

The President
September 27, 2016
Page 5 of 5

Findings and Conclusion

The CDC conducted a thorough investigation into Dr. Lanciotti's allegations, and its findings appear reasonable. However, Dr. Lanciotti raises serious concerns about each of the CDC's findings, including the methodology for discounting his research and that conducted by BSRI, both of which suggest that the Trioplex may detect fewer Zika infections than the Singleplex.

I acknowledge the CDC's ongoing efforts to improve the analytical sensitivity of the Trioplex, including the EOC's August 22, 2016 proposal to substantially amend the Trioplex EUA. As the agency contemplates additional improvements or changes to the Zika testing protocol, I encourage CDC to review Dr. Lanciotti's comments, respond to each of his concerns, and utilize his expertise as the agency works to ensure it is implementing the most effective testing methods in response to this public health emergency.

As required by 5 U.S.C. § 1213(e)(3), I am now transmitting the agency report and the whistleblower comments to you and to the Chairmen and Ranking Members of the Senate Committee of Health, Education, Labor, and Pension, and the House Committee on Energy and Commerce. I have also filed copies of this letter, the agency report, and the whistleblower comments in OSC's public file, which is available online at www.osc.gov. This matter is now closed.

Respectfully,



Carolyn N. Lerner

Enclosures