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Counterpoint: *Early warning systems are imperfect, but essential*

Christine Y Lu, MSc, PhD,

Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, 401 Park Drive, Suite 401 East, Boston, MA 02115

Gregory Simon, MD, MPH,

Group Health Research Institute, 1730 Minor Ave #1600, Seattle, WA 98101

Stephen B Soumerai, ScD, and

Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, 401 Park Drive, Suite 401 East, Boston, MA 02115

Martin Kulldorff, PhD

Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, 1620 Tremont Street, Suite 3030, Boston, MA 02120

Abstract

Sequential analysis can be used as an early warning system about potential unintended consequences of health policy decisions, generating follow-up investigations, but it should not be used as causal evidence.

We thank Dr. Stone for his interest in our methodological proof-of-concept paper on near real-time surveillance of the effect of drug policy decisions.¹ Most of his commentary is about the causal question discussed in our other paper that was published in the British Medical Journal in 2014.² For example, Dr. Stone comments at length about interrupted time series analyses, which was not used in our surveillance paper. In this counterpoint we only address the few issues directly relevant to our methodological surveillance paper, while the comments on the BMJ paper are extensively discussed in a second, separate Counterpoint.³

Dr. Stone gives an inaccurate description of the nature and purpose of the sequential analysis we conducted. For example, he states that the results from the sequential analysis “*suggest an increase in psychotropic drug poisonings among adolescents did occur but not until the fourth quarter of 2007, four years after the initial advisories...*” When using a sequential probability ratio test, it is typically assumed that the risk remains constant from the start until the end of surveillance, and the method will signal, not when a change occurs, but when sufficient amount of data has accumulated such that the sample size is big enough to detect a signal.. For instance, the purpose of sequential analysis, as commonly used in

clinical trials, is not to detect if and when drug A is better or worse than drug B, but to signal when there is enough evidence to suggest that drug A might be better or worse than drug B. So, the fourth quarter of 2007 indicates the time when there was enough data to suggest that there may be an increase in psychotropic drug poisonings but the increased risk is assumed to have existed before that time. That is, the policy change and the outcome change is assumed to happen at around the same time, but the latter can only be detected some months or years later, when sufficient sample size has accrued. If one instead desires to detect the time of a change, one cannot and should not use sequential probability ratio tests; instead, one should use other methods such as change point analysis or cumulative sum control chart methods.^{4, 5}

Dr. Stone is correct that selecting the temporal trend to use for the null hypothesis is critical. However, the point is not to accurately predict that future trend, which is very difficult if not impossible, nor is it relevant for near-real time surveillance. Instead, it should be selected to be the future trend from which one wants to detect a divergence if there is one. For example, even if we predict that the future trend will stay flat, we may only be interested in detecting an increase that is more than 2% per year, or we may predict that there will be an increase, but still want to detect any increase beyond a flat 0% trend.

Dr. Stone questions the use of the sequential analysis method for providing “evidence for a cause.” We agree (and stated this point repeatedly in the paper), and it is critically important to note that if and when the surveillance system generates a signal, it is merely an indication that something might be wrong. Near-real time surveillance should never be used as the definite or best proof about causal relationships. It should only be used as an early warning system that something might be wrong which warrants further investigation using traditional scientific designs. Specifically, our surveillance paper should not be used as contributing evidence either for or against the hotly contested issue of whether the FDA warnings and media coverage about antidepressants led to an increase in suicide attempts. Discussion about that issue should be based on more rigorous study designs (see our second counterpoint), and this methodological paper has nothing additional to contribute to that question. What we showed in this paper is that if near real-time monitoring had been in place immediately after the regulatory actions and media coverage, we would have detected a potential problem much sooner. Rigorous quasi-experimental studies could then have commenced earlier, providing more timely clinical and public health information.

Sequential analysis has long been used for clinical trials and more recently for drug and vaccine safety surveillance.⁶⁻⁸ As for the utility of using sequential statistical analysis to conduct near real-time surveillance to monitor the effect of health policy changes, only time will tell how much it can contribute to public health. Based on this methodological study, we are optimistic that it will. Nevertheless, there are challenges. As we emphasize in the paper, we believe that systematic evaluation of responses to health policies may include “sequential analysis to quickly and efficiently detect signals... that can then be thoroughly investigated in rigorously designed studies.”¹

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References

1. Lu CY, Penfold RB, Toh S, et al. Near real-time surveillance for consequences of health policies using sequential analysis. *Med Care*. 2017
2. Lu CY, Zhang F, Lakoma MD, et al. Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study. *BMJ*. 2014; 348:g3596. [PubMed: 24942789]
3. Lu CY, Simon G, Soumerai SB. Staying Honest When Policy Changes Backfire. *Med Care*. 2017
4. Chen, J., Gupta, AK. Parametric Statistical Change Point Analysis: With Applications to Genetics, Medicine, and Finance. New York: Springer Science+Business Media; 2012.
5. Page ES. Continuous Inspection Schemes. *Biometrika*. 1954; 41:100–115.
6. Jennison, C., Turnbull, BW. Group Sequential Methods with Applications to Clinical Trials. Boca Raton: Chapman & Hall/CRC; 2000.
7. Lieu TA, Kulldorff M, Davis RL, et al. Real-time vaccine safety surveillance for the early detection of adverse events. *Med Care*. 2007; 45:S89–95. [PubMed: 17909389]
8. Yih WK, Kulldorff M, Fireman BH, et al. Active surveillance for adverse events: the experience of the Vaccine Safety Datalink project. *Pediatrics*. 2011; 127(Suppl 1):S54–64. [PubMed: 21502252]