Monitoring and Assessment of Medical Countermeasures as Part of a Public Health Emergency Response

Ensuring the availability of safe and effective medical countermeasures (MCMs) is an essential part of any emergency response involving a chemical, biological, radiological, nuclear, or emerging infectious disease threat. For more than a decade, the US government has developed and refined the capabilities necessary to rapidly distribute, dispense, and administer MCMs—what many traditionally call "the last mile." However, full-lifecycle surveillance to monitor MCM use and assess safety and effectiveness during an emergency response has not kept pace with preparedness efforts. The US government has a limited capacity to rapidly collect, share, and analyze MCM data in real-world settings.

Effective MCMs are critical to minimize morbidity and mortality when responding to chemical, biological, radiological, nuclear, or emerging infectious disease threats, so it is important to accurately assess their impact. Research must be incorporated into public health emergency response.[1] Many MCMs may be used for the first—and possibly only—time in the affected population during an emergency. Though emergency preparedness efforts have improved considerably, MCM-related planning is hindered by the inability to effectively monitor the use, safety, and effectiveness of MCMs in real-world settings.

The success of an emergency response will depend on the trust and demands of the public, clinicians, and state and local health responders. To safeguard that trust, the US government must be confident that MCMs are performing as expected without causing additional harm. The current emergency response framework, including the infrastructure for MCM dispensing and administration, must be leveraged without disrupting patient care and emergency response efforts. That is the only way to go beyond "the last mile" to truly assess whether an MCM helped, harmed, or had no effect.

ASSESSMENT IN A PUBLIC HEALTH EMERGENCY

The traditional lifecycle for medical products usually follows a structured and iterative process. In each case, the US Food and Drug Administration (FDA) reviews all available evidence to decide whether to approve, license, or clear a product. To the extent possible, MCMs follow this pattern. However, MCMs present unique challenges because they may be made available in varying stages of research and development.

In response to recent public health threats, medical products have been made available earlier in the development stage than ever before, forcing researchers to try to collect premarket data in a postmarket-type setting. In response to the 2009 H1N1 influenza pandemic, researchers were unable to assess the clinical effectiveness of intravenous peramivir, an unapproved drug made available under an Emergency Use Authorization.[2] Although an Emergency Use Authorization provided access to peramivir, use of a product under this authorization yields little data beyond standard adverse event reporting. Randomized controlled clinical trials remain the most efficient and reliable way to assess safety and effectiveness of all medical products. Throughout the 2014–2015 Ebola virus disease outbreak in West Africa, the FDA maintained that randomized controlled trials that incorporate advances in trial design could yield needed safety and effectiveness data in an ethical way.[3] But randomized controlled trials can be challenging to plan and conduct during an emergency.

The emergency landscape is not conducive to rapid MCM assessment. There are significant differences between assessment during a public health emergency and traditional research and development (Table 1), so it is critical to establish a middle lane to bridge this gap. The shortcomings of past MCM data collection efforts were attributable, in part, to a lack of planning and experience. Historically, MCM assessment in such situations did not occur, nor was it expected, given the vast limitations posed by a public health emergency environment. However, enabling MCM assessment is necessary to improve preparedness for future emergencies. If, for example, protocols were developed and pre-positioned across a network of clinical sites in a way that allows real-time MCM data

ABOUT THE AUTHORS

Gregory T. Measer and Jean Hu-Primmer are with the Office of Counterterrorism and Emerging Threats, Office of the Chief Scientist, US Food and Drug Administration (FDA), Silver Spring, MD. Carmen T. Maher is a retired US Public Health Service Commissioned Corps officer formerly affiliated with the FDA.

Correspondence should be sent to Gregory T. Measer, Regulatory Counsel, US Food and Drug Administration, Office of Counterterrorism and Emerging Threats, 10903 New Hampshire Ave, Silver Spring, MD 20993 (e-mail: gregory.measer@fda.hhs.gov). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

This editorial was accepted May 4, 2018.

Note. *This article reflects the views of the authors and should not be construed to represent the US Food and Drug Administration's views or policies.*

doi: 10.2105/AJPH.2018.304526

TABLE 1—How Is Assessment Different in a Public Health Emergency?

	Public Health Emergency	Traditional Research and Development
Intent	Respond and mitigate	Generalizable knowledge
Planning	Unplanned or unexpected	Planned or deliberate
Data collection	Uncontrolled or no data collection	Well-controlled clinical trials
Environment	Undefined number of individuals Simultaneous administration and potential use of multiple products Requires rapid decision-making	Defined number of individuals Stepwise progression and single product administration Allows more time for decision-making
Oversight	Little or no tracking or monitoring Lack of or limited clinical provider interaction	Strict oversight and monitoring Principal investigator and clinical study staff interaction Informed consent and institutional review board
Reporting	Limited reporting and information sharing	Clearly defined reporting requirements and information sharing

collection and analysis, then MCM assessment could be coordinated alongside distribution, dispensing, and administration. Incorporating MCM assessment as an essential component in the emergency preparedness framework is crucial, but will take considerable time and effort.

A CALL TO ACTION

There are significant challenges to building the infrastructure necessary to assess MCMs, including technical, legal, administrative, logistical, and financial. There is also the question of leadership and sustainability at the federal level, with so many agencies across the Public Health Emergency Medical Countermeasures Enterprise[4] playing important roles in MCM preparedness and response. Most importantly, any infrastructure that is leveraged or built to assess MCMs must be capable of performing this evaluation without disrupting ongoing patient care and emergency response efforts.

Despite the work ahead, there is tremendous opportunity now to leverage existing efforts. Driven by advancements in electronic health data and real-world evidence generation, the current data infrastructure presents an opportunity to inform clinical use of MCMs without placing undue burden on the health care system. These initiatives have been spearheaded by FDA efforts such as the Sentinel Initiative, the National Evaluation System for Health Technology, and the Real-Time Application for Portable Interactive Devices platform. With the recent passage of the 21st Century Cures Act, the FDA will continue to support innovations in medical product development and facilitate the use of real-world evidence in regulatory decision-making.[5] Though traditional randomized controlled trials remain the gold standard for medical product assessment, there is a need for new and novel ways to collect and analyze data for scientifically sound evaluation of MCMs.[6]

Collecting and using data in a more efficient way requires more than just infrastructure and technology. It requires coordination across all levels of government, among industry and product sponsors, across clinicians who seek to utilize the best-available products to care for patients, and with the public at large. Many assume that this work is already ongoing, and to some extent it is, through traditional medical product safety surveillance. However, there is no dedicated infrastructure that addresses the assessment gaps in the unique MCM environment.

Discussions on how to deal with the specific assessment challenges facing MCMs are ongoing via a Public Health Emergency Medical Countermeasures Enterprise interagency workgroup. Medical countermeasure monitoring and assessment issues were also the subject of a recent National Academies of Sciences, Engineering, and Medicine workshop sponsored by the FDA.[7] These discussions have highlighted a remarkable opportunity to close the MCM assessment gaps through increased coordination and collaboration beginning at the federal level. However, the US government cannot do this alone. Input and engagement from all interested stakeholders before an emergency is critical to ensure an effective MCM response.

CONCLUSION

In a perfect world, everyone would know everything about every product and its effects on every individual before approval and use. Given the abundance of electronic health data and a growing infrastructure to analyze these data, building a national capability to monitor and assess MCMs during emergencies is possible. However, it will take time to shift public health response beyond rapid distribution, dispensing, and administration. The entire public health community must also leverage existing efforts without overburdening clinical care and emergency response. Important work has been done to provide needed MCMs to the public. Now we must all work to ensure we have the capability to rapidly assess whether they help, harm, or have no effect. AJPH

Gregory T. Measer, JD
Carmen T. Maher, MA, BSN, RN, RAC
Jean Hu-Primmer, MS

CONTRIBUTORS
All authors contributed equally to this article.

REFERENCES

1. Lurie N, Manolio T, Patterson AP, Collins F, Frieden T. Research as a part of public health emergency response. *N Engl J Med*. 2013;368(13):1251–1255.

2. Yu Y, Garg S, Yu PA, et al. Peramivir use for treatment of hospitalized patients with influenza A(H1N1)pdm09 under

emergency use authorization, October 2009–June 2010. *Clin Infect Dis*. 2012; 55(1):8–15.

3. Cox E, Borio L, Temple R. Evaluating Ebola therapies—the case for RCTs. *N Engl J Med*. 2014;371(25): 2350–2351.

4. US Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response. Public Health Emergency Medical Countermeasures Enterprise. 2017. Available at: https://www.phe.gov/Preparedness/mcm/phemce/Pages/default.aspx. Accessed March 27, 2018.

5. US Food and Drug Administration. 21st Century Cures Act. 2017. Available at: https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/21stCenturyCuresAct/default.htm. Accessed December 26, 2017.

6. Borio L, Cox E, Lurie N. Combating emerging threats—accelerating the availability of medical therapies. *N Engl J Med*. 2015;373(11):993–995.

7. National Academies of Sciences, Engineering, and Medicine. *Building a National Capability to Monitor and Assess Medical Countermeasure Use During a Public Health Emergency: Going Beyond the Last Mile: Proceedings of a Workshop*. 2017. Available at: http://www.nationalacademies.org/hmd/Reports/2017/building-a-national-capability-to-monitor-and-assess-MCM-use-during-a-PHE-proceedings.aspx. Accessed December 26, 2017.