



HHS Public Access

Author manuscript

Health Secur. Author manuscript; available in PMC 2020 February 06.

Published in final edited form as:

Health Secur. 2019 ; 17(1): 46–53. doi:10.1089/hs.2018.0092.

EVALUATING **P**ROMISING **I**NVESTIGATIONAL **M**EDICAL **C**COUNTERMEASURES: **R**ECOMMENDATIONS IN THE ABSENCE OF **G**UIDELINES

Nahid Bhadelia [Medical Director],

Special Pathogens Unit, Section of Infectious Diseases, Boston University School of Medicine,
Boston, MA

Lauren Sauer [Assistant Professor],

Director of Research, Johns Hopkins Biocontainment Unit, Department of Emergency Medicine,
Johns Hopkins Medicine, Baltimore, MD

Theodore J. Cieslak [Associate Professor],

Department of Epidemiology, University of Nebraska College of Public Health, Omaha, NE

Richard T. Davey [Deputy Clinical Director],

Division of Clinical Research, National Institute of Allergy and Infectious Diseases, Bethesda, MD

Susan McLellan [Medical Director],

Biocontainment Treatment Unit, Division of Infectious Diseases, University of Texas Medical
Branch at Galveston, TX

Timothy M. Uyeki [Chief Medical Officer],

Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for
Disease Control and Prevention, Atlanta, GA

Mark G. Kortepeter [Professor]

Department of Epidemiology, University of Nebraska College of Public Health, Omaha, NE

**National Ebola Training and Education Center's Special Pathogens Research Network
(SPRN)'s Medical Countermeasures Working Group**

Abstract

Emerging and re-emerging infectious diseases pose growing global public health threats. However, research on and development of medical countermeasures (MCMs) for such pathogens is limited by the sporadic and unpredictable nature of outbreaks, lack of financial incentive for pharmaceutical companies to develop interventions for many of the diseases, lack of clinical research capacity in areas where these diseases are endemic, and the ethical dilemmas related to conducting scientific research in humanitarian emergencies. Hence, clinicians providing care for patients with emerging diseases are often faced with making clinical decisions about the safety and effectiveness of experimental MCMs, based on limited or no human safety, preclinical, or even

Address correspondence to: *Nahid Bhadelia, MD, MALD, Medical Director, Special Pathogens Unit, Boston Medical Center and Assistant Professor, Section of Infectious Diseases, Boston University School of Medicine, Boston, MA, nbhadel@bu.edu.*

The views expressed are solely those of the authors and do not necessarily reflect the official position of the University of Nebraska or its affiliates, the Centers for Disease Control and Prevention or the National Institutes of Health, the Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response, or the US government.

earlier product research or historical data, for compassionate use. Such decisions can have immense impact on current and subsequent patients, the public health response, and success of future clinical trials. We highlight these dilemmas and underscore the need to proactively set up procedures that allow early and ethical deployment of MCMs as part of clinical trials. When clinical trials remain difficult to deploy, we present several suggestions of how compassionate use of off-label and unlicensed MCMs can be made more informed and ethical. We highlight several collaborations seeking to address these gaps in data and procedures to inform future clinical and public health decision making.

Keywords

Medical countermeasures; Emerging infectious diseases; Outbreaks; Ebola; Drug development; Ethics

SIR WILLIAM OSLER ONCE commented that “medicine is a science of uncertainty and an art of probability.”¹ In the realm of medical uncertainty, the care of patients with uncommon but emerging and high-impact infectious diseases occupies a unique place. Treatment is often hampered by limited understanding of the pathogen and little objective data on clinical progression and optimal supportive care. The few therapeutic candidates that exist frequently have limited efficacy data in humans. Outbreaks of such diseases are occurring with greater frequency because of increasing population and migration, trade and travel, and environmental factors, creating an urgent need for ways to efficiently develop, compare, and prioritize targeted medical countermeasures (MCMs).²

The diseases under consideration here are those that occur relatively rarely but have the potential for easy transmissibility in a population (including to healthcare workers and researchers) and high mortality (eg, the hemorrhagic fevers, emerging respiratory pathogens). Several factors serve as hindrances to the development and testing of MCMs for such pathogens. First, outbreaks occur sporadically and frequently in resource-poor areas with limited infrastructure for either translational research or advanced clinical care. Second, these potentially highly transmissible pathogens require formative research to be conducted in biosafety level-4 (BSL-4) labs, which are few in number and exist mostly in resource-rich countries.^{3,4} Finally, the sporadic nature of market demand and the low resources of the populations at risk translates to inconsistent public and commercial interest in financing the development of MCMs.⁵ The conventional “gold standard” for rigorous safety and efficacy testing of MCMs is the randomized controlled trial, and licensure from the US Food and Drug Administration (FDA) is typically given based on evidence from randomized controlled trials. Such trials are lengthy and expensive. Public interest and political will to fund development of MCMs for diseases of interest may be high during an outbreak but wane once the outbreak has ended.⁶

Therefore, during an outbreak, clinicians and health authorities often find themselves learning about the manifestations, pathophysiology, outcomes, and sequelae of these infections at the same time that they are trying to make sensible clinical and policy decisions regarding appropriate MCMs. With few or no licensed therapies with good efficacy data available, clinical providers considering investigational MCMs must interpret presumed

safety and efficacy from preclinical studies that may or may not translate well to humans. The evaluation of the evidence and prioritizing options, in some situations, may be led by the individual clinician or organization that is actively treating patients, leading to a request to the appropriate regulatory authority to authorize the use of specific investigational MCMs, rather than a more typical scenario in which the regulatory agency chooses which MCMs to authorize based on previously available data. In such conditions, the use of the MCM is frequently authorized under a compassionate use protocol, without strict requirements for standardized practices or data collection. Decisions on which MCMs to use, and how, may thus vary widely between clinicians and institutions, contributing to inconsistent interpretation of outcomes.

Here we highlight the clinical and ethical challenges associated with evaluating experimental treatments for emerging infectious diseases of major public health concern under conditions of unpredictable clinical need, limited pre-existing data, and poor infrastructure for clinical research. We also underscore the importance of ongoing proactive investments and efforts to push MCM development from the preclinical stage to human testing in randomized controlled trials so as to reduce future need for the compassionate use mechanism. We outline several approaches that could facilitate the prompt initiation of rigorous drug trials when an outbreak appears. If it is not feasible to develop rigorous randomized controlled trials for certain MCMs, we recommend that more organized and stringent preclinical and operational approaches be developed to evaluate the potential benefits and hazards of experimental MCMs planned for compassionate use. Underpinning all of these recommendations is a call for ethical and operational guidelines on how MCMs in various stages of development should be evaluated, existing data gathered and analyzed, prospective data collected, and further research prioritized. Lastly, we share examples of organizations and collaborations attempting to address the issues above and present some insights about procedures that could be recommended in the absence of guidelines.

A NEED FOR GUIDELINES AND RECOMMENDATIONS

The 2013–2016 Ebola virus disease (EVD) epidemic in West Africa provides a poignant illustration of the central dilemmas presented above. Numerous investigational MCMs were given under emergency use authorization in West Africa, the United States, and Europe during the 2013–2016 epidemic. Without any FDA-approved targeted MCMs, and in the setting of a growing public health crisis, there were renewed international calls for investment in the development of novel therapies and increased availability of experimental treatments in the field. A World Health Organization (WHO) panel concluded that there was an “ethical imperative” to make therapies with promising preclinical data available to patients with EVD.⁷ Many experts and much of the lay public felt that patients with EVD had a right to experimental treatments because of the high mortality of the disease and at least some reasonable expectation of benefit.^{8,9} Conversely, others in the scientific community argued that insufficient data existed to guarantee benefit from any of the MCMs being considered, and that there was even potential for harm.¹⁰ Significant international discussion also ensued during that epidemic about whether a traditional randomized controlled trial was ethical in an outbreak setting.

The experience from this epidemic showed that, although responding to public calls for access in the absence of rigorous trials, both the off-label use of licensed products and the compassionate use of unlicensed products had undetermined benefit and possible harm for patients and provided little additional, generalizable scientific knowledge. This is because, first and foremost, the emergency use of off-label or experimental MCMs blurs the line between research and clinical care—that is, purposes that can have fundamentally different outcomes. Largent argued that “whereas medical care focuses on providing optimal care to individual patients, clinical research is primarily concerned with producing knowledge for the benefit of future patients.”^{11(p502)} And yet, due to the sporadic presentation of EVD cases, the WHO panel recommended that data should be gathered for scientific inquiry during emergency use of investigational therapeutics where possible, as long as their use was equitable and there was monitoring for adverse effects.⁷

The use of an approved therapeutic for an off-label indication is not covered by the same regulatory agencies as is the use of experimental agents available through compassionate use, but both approaches can easily result in a situation of essentially unregulated research. Neither offer the stringent human subject protections, clinical equipoise, and research oversight generally applied to formal clinical trials.

In the case of off-label use in the United States, clinicians are allowed to use their judgment in offering any licensed drug or other MCM for an indication for which it has not been FDA approved (off-label use). The FDA advises physicians to use scientific rationale and medical evidence to guide such use. When US physicians fail to do this, their conduct and its consequences fall under the jurisdiction of state medical licensing boards. Adverse outcomes also raise the threat of malpractice actions by patients or patients’ families unhappy with those outcomes.¹¹

But what about in the middle of an outbreak in a resource-limited setting? The West African EVD epidemic highlighted this dilemma, when certain Ebola treatment units repurposed available drugs approved for other indications for off-label use in EVD patients.^{12,13} In one case, approximately 100 consecutive patients were given atorvastatin and irbesartan as a targeted MCM against Ebola under the compassionate use mechanism. Results were reported without formal documentation of the standard of care received by those patients or of their mortality outcomes.¹⁴ Such informal implementation and reporting of an experimental off-label use of an approved drug highlights the challenges of ensuring that product use in resource-limited settings meets the rigorous reporting requirements for such use expected in a developed setting. Richardson et al report a wide disparity among the studies eventually published on the West Africa EVD epidemic and ambiguity as to whether internationally recognized ethical criteria were met.¹³

In the case of compassionate use of a nonapproved agent, who should make the decision of how much data are sufficient to allow use in humans? In non-outbreak settings, there is generally a joint decision-making process between FDA regulators and treating physicians and institutions, as has occurred for many laboratory-acquired infections and exposures to emerging pathogens.¹⁵ In resource-limited settings and during an outbreak, the decision to import an unapproved MCM falls to the regulatory agencies of national governments. The

process may be initiated by specific requests from clinicians or organizations, or it may be led by an international agency such as the WHO, which developed the MEURI process (Monitored Emergency Use of Unregistered and Investigational Interventions) for the current epidemic in the North Kivu region of the Democratic Republic of the Congo (DRC). The WHO convened experts to recommend specific MCMs and facilitated the national authority's ability to provide certain agents to treatment units.¹⁶ The eventual use in an individual patient is still often determined by treating clinicians or their specific organization.

In all of these settings, MCMs are often administered in drastically different clinical settings with different standards of care, as was the case in the West African epidemic, and sometimes by care providers with minimal prior experience in providing EVD-related care, making any data largely ungeneralizable.^{17,18} Even when background standard of care was more or less equivalent, such as for most of the 27 EVD patients cared for in the United States and Europe during 2014–15, use of investigational therapeutics without comparative protocols or controls made it difficult to determine the relative benefits or harm from the products.^{3,19,20}

Lastly, in resource-limited settings, nonstandardized investigational use can cause further harm if it “consumes scarce healthcare resources” for the current patient or diverts public health funds for future patients with uncertain evidence of benefit.¹¹ The small samples sizes could also obscure potential harm that may not become evident until a drug is used in much larger populations under more standardized conditions.

Eventually, several experimental therapies were deployed for testing in the West Africa outbreak in either traditional randomized designs or with modified study structures that included use of 2 different therapeutics in different study arms rather than placebo. However, by the time formal protocols were put in place, the epidemic had begun to recede, leaving trials under-enrolled and under-powered. The yield of scientific knowledge on investigational countermeasures backed by robust data was distressingly thin.²¹ In addition, in many situations, the initiation of therapeutic protocols in an Ebola treatment unit was accompanied by enhancement of laboratory diagnostic capacity, increased available personnel, and more consistent provision of nonspecific supportive care. Hence, improved outcomes may have resulted from improvement in the baseline standard of care under research conditions, rather than from a specific therapeutic agent. More disconcerting, apparently equivocal results may have masked what could have been a deleterious effect of the agent.^{22,23} This scenario highlights the benefit of a placebo arm with the highest level of supportive care, despite some of the ethical arguments against it.

In the aftermath of the epidemic, many subject matter experts argued that to generate actionable evidence of effectiveness on new MCMs, their deployment must occur in a trial setting with a clear scientific question and with human subject protections inherent in this type of research.^{17,21} What steps can be proactively taken to ensure that MCMs are ready for trial when an outbreak occurs?

BEYOND COMPASSIONATE USE

As with many emerging infectious diseases, although we may not know where the next Ebola or Marburg disease outbreak will occur, we can say with near certainty that future outbreaks *will* occur. The recent experiences with EVD epidemics illustrate that we cannot get definitive efficacy data without randomized controlled trials. Implementing such trials with the speed necessary to capture data in an outbreak can occur only if prioritization and protocols are in place before it begins.¹⁷ Consistent funding streams through international and government agencies to support of this type of research has previously been identified as a critical component of readiness and is not discussed at length here.^{24,25}

Several scientific and organizational steps could improve preparedness of the international community to successfully conduct clinical research in an outbreak:

- **Setting international research and public health priorities for diseases in need of further clinical research:** In advance of drug development, the international community can identify those (re)emerging infectious diseases that constitute priorities for further clinical research. The WHO R&D blueprint helped pave the path toward this goal.²⁶ WHO employed a multi-step approach that included the development of a methodology to identify a list of priority diseases, the introduction of an annual review of the list, and the development of a decision-making guide on inclusion of novel diseases.²⁷
- **Advancing the preclinical agenda:** When human cases are rare and experimental infection in humans for research purposes is not an acceptable option, animal models are the usual way to develop knowledge of how MCMs might perform in humans. Unfortunately, our current understanding of comparative safety and efficacy of different MCMs is greatly limited by an incomplete preclinical and animal testing database. Further, animal models do not always reflect typical routes of human exposure and infection or the history of disease in humans.²⁸ In terms of comparing agents, most of the existing MCMs for EVD were developed independently and were rarely evaluated by identical methodologies or with the same set of experiments. Meanwhile, studies of combination therapy—one of the modern hallmarks in treating viral diseases—is almost totally lacking with these countermeasures. It is virtually impossible to determine whether some combinations of these agents might display synergy, antagonism, or indifference among each other or with drugs used routinely in clinical care.

For these reasons, there is a compelling need for organizations to work collaboratively to support meaningful animal (particularly nonhuman primate) studies to address the identified knowledge gaps in advance of future outbreaks. Current animal models should be refined so that combination treatment strategies can be properly evaluated. Drug manufacturers should work closely with collaborating researchers hoping to bring an MCM to market to ensure that intellectual property rights are protected and that concerns about competition for a pathway to product licensure will not hamper such collaboration.

- **Prioritization of MCMs to be tested in an emergency:** Transparent and collaborative discussions regarding which MCMs are available, have promise, and would be ideal for testing during the next inevitable outbreak are needed for optimal resource expenditures by governments and public health bodies. In 2014, the National Institute of Allergy and Infectious Diseases (NIAID) and the FDA gathered a group of researchers, clinicians, regulators, and other subject matter experts to develop a common strategy for clinical research on countermeasures for EVD over 2 separate workshops.¹⁷ The workshops allowed presentation of up-to-date evidence on countermeasures (published and unpublished) and a discussion of those that it would be clinically acceptable and logistically possible to test in the field. Through a consensus-building process, participants prioritized MCMs that showed promise and readiness for randomized controlled trial deployment. Additionally, the workshops created consensus for a ‘‘master protocol’’ with an adaptive format of clinical randomized controlled trials that integrated investigational therapies combined with an optimized standard of care versus the latter alone.

The methodology employed in these workshops was established through prior meetings among expert groups to determine the care and treatment of researchers exposed to filoviruses while working in BSL-4 laboratories.²⁹ These examples can provide a model for how collaborative evaluations and prioritization of MCMs could be conducted.

- **Implementing agreements between governments and public health authorities prior to an emergency:** In the recent EVD outbreak in the North Kivu region of the DRC (August 2018), WHO’s proactive work to gain in-country approval for investigational product compassionate use that began in the prior outbreak in the DRC’s Equateur Province proved useful.³⁰ As a result, WHO was able to facilitate the availability of investigational MCMs (1 vaccine, 4 therapeutics) under compassionate use with the MEURI protocol discussed above early in the outbreak while undertaking planning for a randomized controlled trial. The use of existing agreements with ministries of health and off-the-shelf compassionate use protocols is a good model for the future. However, using such protocols alone may only provide anecdotal evidence of safety and efficacy, if not accompanied by more robust comparative clinical trials. The existence of this collaboration is now leading the way toward a randomized controlled trial of 3 investigational drugs sponsored by NIAID that will be not only multicenter but also span over multiple outbreaks, allowing for early trial initiation during the next outbreak.³¹
- **Supporting local research capacity:** The development of host country research capacity, including the fostering of national researchers and the establishment of diagnostic and research laboratories prior to the onset of an outbreak, is vital to the promotion and conduct of research in resource-limited countries.^{32,33} It would be reasonable to tailor such capacity-building efforts to the epidemiologic distribution of the diseases considered as high priority.

- Improving and standardizing supportive clinical care:** Finally, in order to ethically justify any randomized controlled trials with a placebo arm, clinicians and researchers need confidence that they are providing the best supportive care possible in all study arms, including the placebo arm. In the case of filoviruses, for which most care has been given in highly constrained and under-resourced settings, many questions remain about optimal nonspecific supportive management of patients with EVD.^{34,35} However, it is likely that the increased survival rate of infected responders who were evacuated to highly resourced care facilities was in part due to intensive supportive care.³ By improving the delivery of supportive care (and researching what constitutes best supportive care for specific diseases), we may also reduce mortality and hence make the allure of untested products less compelling for physicians and patients during these outbreaks.³⁶ Additionally, it is ethically important that we strive to close the gap in capacity for intensive supportive care between resource-rich and -limited settings. This is particularly important for those pathogens that pose a significant risk to healthcare workers. The provision of high-quality supportive care is often deferred during the initial phase of an outbreak while awaiting establishment of safe facilities and personal protection protocols.³⁷ However, building research capacity in resource-limited countries may aid in timely allotment of high-quality of care. Because conducting clinical research typically requires some degree of laboratory support and a reliable standard of available clinical care, including research as a part of the clinical care enterprise complements both activities: Treatment facilities that provide excellent baseline care are necessary for the conduct of clinical research in an outbreak, and laboratories put in place for research can also provide clinically useful data in real time to support the care of ill patients.

DECISION MAKING WHEN EVIDENCE IS LIMITED

Despite efforts to further an organized research agenda that can yield data with scientific rigor, there will likely still be situations in responding to outbreaks where well-meaning clinicians will need to consider the use of experimental MCMs under compassionate use. What recommendations should clinicians follow for choosing among potential MCMs, how can they collect clinical data in a way that will contribute meaningfully to the knowledge base, and when should experimental therapies be re-prioritized or abandoned?

- Deciding between MCMs in development:** The development of summaries of potential countermeasures would be useful in assisting clinicians to make expeditious decisions on which products might best benefit their patients. WHO posted such a summary on their website during the 2013–2016 West Africa outbreak.³⁸ The National Ebola Training and Education Center (NETEC) is a consortium of 3 medical facilities (University of Nebraska Medical Center, Emory University Hospital, and New York Bellevue Hospital) that cared for EVD patients during the 2013–2016 outbreak.³⁹ NETEC has established a Special Pathogens Research Network (SPRN) among 10 regional biocontainment units in strategic locations across the country. An MCM working group within

SPRN is working proactively to develop similar summaries on diseases with the potential to cause outbreaks and that lack licensed countermeasures, with the goal of posting the summaries for care providers within and outside the SPRN to access. The reviews prioritize promising MCM and other treatment options in more advanced stages, but document options at all points in the pipeline, and are updated regularly as evidence and guidance change.

The group has prioritized the following pathogens for initial summaries: Marburg virus, MERS virus, Lassa virus, Crimean Congo hemorrhagic fever (CCHF) virus, Nipah virus, and smallpox/monkeypox viruses, based on epidemic potential, lack of licensed countermeasures, and recurrences in local or regional outbreaks. An updated tabular summary for Ebola virus is also being developed. Such efforts need to be updated with regular frequency and developed collaboratively with researchers, clinicians, and public health representatives. As the literature relevant to some of these diseases continues to evolve at a rapid pace, maintaining up-to-date summaries will be a challenge. To be immediately useful, the results of these efforts need to be made accessible for clinicians in both resource-rich and resource-limited settings.

- **Assessing appropriate quantity and quality of data for clinical use:** The FDA has provided the animal rule pathway to licensure for products for which human randomized controlled trials may not be feasible. However, there is not clear consensus on how to assess data from animal models or limited observational data from human cases.⁴⁰ What level of evidence (ie, in vitro, small animal, nonhuman primate, or human) is “enough” to arrive at valid conclusions, and how much data are sufficient to allow for more than just limited compassionate use in an outbreak setting? Ideally, a standardized data collection set could be developed, after input from regulators and subject matter experts, for use by all clinicians using experimental MCMs to allow for aggregation of data collected from individual cases.
- **Developing guidelines for ethical use of investigational therapeutics and the ability to perform a rapid ethical analysis during emerging infectious disease outbreaks:** The summaries of evidence on potential MCMs for different diseases (as discussed above) can help fulfill part of the data gap. However, accessible guidelines also need to be developed around the ethics of compassionate use in outbreaks, including the possible benefits and the risks of unanticipated harm. In many circumstances, the compassionate use of MCMs in emergencies can be an ethical grey area, owing at least in part to variations in ethical norms across the response. A real-time ethical analysis with stakeholders, including clinicians, researchers, and members of the affected population or community, and public health practitioners may be a supporting approach to assessing evidence and implementing new guidelines. An independent, culturally contextualized ethics consultation may provide a beneficial reality check regarding appropriate assessment of MCM data and, in turn, clinical use. Community sensitization of known MCMs ahead of an outbreak with the support of local public health and healthcare practitioners can foster the ability to rapidly

deploy MCMs in the event of developing knowledge during an outbreak and help integrate local interpretations of ethical issues.

- Interval evaluation to determine whether clinical equipoise can still be maintained on experimental MCMs:** Equally important to avoiding harm from treatments that may lack benefits is determining when a treatment has developed enough evidence to be considered “standard of care,” even when not yet licensed and especially if there remain no licensed alternatives. Davey et al outlined an evaluation process for ZMapp during and after the PREVAIL II study.¹⁷ The positive, but not quite statistically significant, results from that trial, in combination with the highly publicized use of the drug for medically evacuated healthcare workers, suggested for most, but not all, subject matter experts that equipoise had shifted toward the positioning of ZMapp for future studies.¹⁷ As may happen with future MCMs, the data evaluated were obtained from a combination of individual compassionate use cases and from standardized trial conditions. Such an evaluative process is more complicated than interpreting data in the setting of a well-powered trial, where a data safety and monitoring board is in place and interim review could provide valuable insight. Disagreement regarding whether agnosticism about the effectiveness of a drug in a study can be maintained also limits buy-in from response organizations and partner countries where trials may be held. The guidelines discussed in the section above could more clearly address the level of evidence sufficient in an outbreak setting to ethically justify continued use of the MCM in question if data are not supportive or, if data are supportive, to continue other studies where the promising drug is not included in the standard of care arm. A similar quandary may also arise when an experimental vaccine becomes integral to the public health response, as has occurred with the recombinant vesicular stomatitis vaccine (rVSV) for *Zaire ebolavirus* in the 2 latest DRC outbreaks in 2018. Based on the successful model employed during the West Africa outbreak, the vaccine has been used both as pre-exposure immunization in healthcare workers and as postexposure prophylaxis of Ebola contacts and healthcare workers.^{41–44} This wide-spread use of the vaccine has implications for testing of other potential immunotherapy-based MCMs for the same indications.

CONCLUSION

The size, scope, and duration of the 2013–2016 West Africa EVD epidemic, combined with the high case fatality proportions and the availability of promising MCMs, led to an opportunity to test those countermeasures in humans and a call to implement the operational use of those countermeasures earlier than in the past. This phenomenon established a new international paradigm for use of experimental therapeutics during an outbreak. Subsequent outbreaks of Ebola and Marburg virus disease have continued along this new model. Other outbreaks of severe diseases that lack licensed countermeasures may follow similar patterns. Given the likelihood of future outbreaks, the continual evolution of our understanding of the diseases themselves, and the development of promising therapeutic candidates in development, the medical community can embrace the opportunity to step back and consider

how best to simultaneously advance knowledge and patient care when these opportunities arise. We have attempted to provide a summary of some key aspects of the challenges being faced and have issued a call to action for the international medical community to work out the processes to apply the new knowledge and determine the best methodologies in advance of the next outbreak.

Acknowledgments

Research reported in this article was supported by funding from the Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response under award number 36-5420-3003-003. We would like to acknowledge all the members of the Special Pathogens Research Network (SPRN) Medical Countermeasures Working Group for their review of the paper, including Mary Akers, Kerry Dierberg, Dan Eiras, Jared Evans, Elena Figueroa, Colleen Kraft, Chris Kratochvil, Karen Martins, Greg Measer, Aneesh Mehta, Jean Hu-Primmer, and George Risi.

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