CBRNE (Chemical, Biological, Radiological, Nuclear, Explosive) Science and the CBRNE Medical Operations Science Support Expert (CMOSSE)

C. Norman Coleman, MD*†; Judith L. Bader, MD*; John F. Koerner, MPH*†; Chad Hrdina, MS*†; Kenneth D. Cliffer, PhD†; John L. Hick, MD†; James J. James, MD, DrPH, MHA[1]; Monique K. Mansoura, PhD, MBA[2]†; Alicia A. Livinski, MPH, MA[3]; Scott V. Nystrom, PhD†; Andrea DiCarlo-Cohen, PhD[4]; Maria Julia Marinissen, PhD†; Lynne Wathen, PhD†; Jessica M. Appler, PhD†; Brooke Buddemeier, MS[5]; Rocco Casagrande, PhD[6]†; Derek Estes, MPA†; Patrick Byrne, AAS, BSN†; Edward M. Kennedy, MS†; Ann A. Jakubowski, MD, PhD[7]†; Cullen Case, Jr, BS[8]; David M. Weinstock, MD[9]†; Nicholas Dainiak, MD[10]†; Dan Hanfling, MD†; Andrew L. Garrett, MD, MPH†; Natalie N. Grant, MPH†; Daniel Dodgen, PhD†; Irwin Redlener, MD[11]; Thomas F. MacKAY, MBA†; Meghan Treber, MS†; Mary J. Homer, PhD†; Tammy P. Taylor, PhD[12]; Aubrey Miller, MD, MPH[13]; George Korch, MD†; Richard Hatchett, MD[14]†*

* CN Coleman, JF Koerner, JL Bader, C Hrdina, R Hatchett had equal contributions to the development of this concept and this paper. Other authors are listed in the order in which their sections appear.

† For authors noted, the contents of this manuscript are their personal and professional opinions and not policy of their agencies or institutions. The content of this article is not the opinion or policy of the U.S. government.

Author Affiliations: Authors are associated with the Office of the Assistant Secretary for Preparedness and Response, U.S. Department of Health and Human Services, Washington, DC, except for those with the following numbered superscripts:

1 Society for Disaster Medicine and Public Health, Inc, Rockville, Maryland, USA

2 MITRE Corporation, Bedford, Massachusetts, USA

3 National Institutes of Health Library, Office of Research Services, Office of the Director, National Institutes of Health, Bethesda, Maryland, USA

4 Radiation and Nuclear Countermeasures Program, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, Maryland, USA

5 Lawrence Livermore National Laboratory, operated by Lawrence Livermore National Security, LLC, U.S. Department of Energy, National Nuclear Security Administration under Contract DE-AC52-07NA27344, Livermore, California, USA

6 Gryphon Scientific, Tacoma Park, Maryland, USA

7 Memorial Sloan Kettering Cancer Center, New York, New York, USA

8 National Marrow Donor Program/Radiation Injury Treatment Network. Minneapolis, Minnesota, USA

9 Dana Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts, USA

10 Yale University School of Medicine, New Haven, Connecticut, USA

11 National Center for Disaster Preparedness, Earth Institute at Columbia University, New York, New York, USA

12 National Security Directorate, Pacific Northwest National Laboratory, Richland, Washington, USA

13 National Institute of Environmental Health Sciences, National Institutes of Health, Bethesda, Maryland, USA

14 Coalition for Epidemic Preparedness Innovations, London, England

Appendix

Introduction

The main paper presents the rationale and proposed content for chemical, biological, radiological, nuclear, and explosives (CBRNE) science and the CBRNE medical operations science support expert (CMOSSE). This concept was developed with extensive input from the co-authors whose experience and detailed description of their responsibilities will be essential going from this concept paper to implementation of the CMOSSE as a disaster medicine expert.

The appendix follows the order of topics shown in Figure 1, with section-by-section details of the seven elements of CBRNE science.

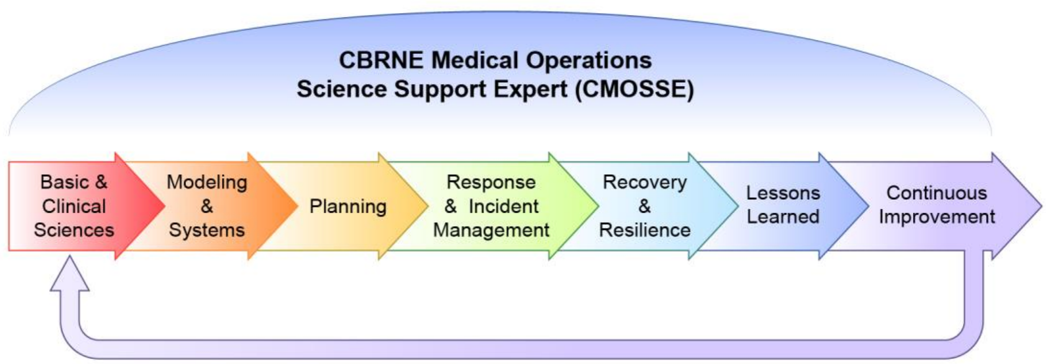


Figure 1: Seven core elements of CBRNE science, overseen by the CMOSSE

Element 1: Basic and Clinical Sciences

General

A prime focus of response activities for incidents that have negative health effects is to obtain the best possible public health and medical outcomes for all involved. Infrastructure matters, but people are the first concern. The “victims” and responders may suffer direct bodily harm, so that lives saved, harm avoided or mitigated, and individual and community resilience are important goals. At-risk populations,[1] which have needs that may affect their ability to obtain medical care, are always considered. Notably, service animals and, as possible, pet animals are also considered. The psychological impacts on people at and beyond the incident site are critical and are discussed in the section on resilience. The chemical, biological, radiological, and nuclear (CBRN) responses each have threat-specific issues. Pressure and crush injuries result from explosives, nuclear detonation, and major structural damage in other types of incidents; therefore, the “E” in CBRNE is cross-cutting. Also of cross-cutting importance is having sufficient resources with optimal co-location of expertise, equipment and supplies, and facilities (“staff, stuff, and space”) with people in need, for specific types of CBRNE incidents and for other large-scale incidents, including those involving accidents or natural disasters.

Medical knowledge includes pathology, physiology, biochemistry, and genetics, with processes in common across injuries, including in accidents or natural disasters, as well as in CBRNE incidents. Important medical issues include, for example, inflammation, immunological changes, and tissue repair and regeneration. Assessing the extent of injury is a component of routine emergency medical care, but specific biomarkers may help determine the type and extent of injury in a CBRNE incident. Development of medical countermeasures (MCMs), including drugs, vaccines, biological agents such as growth factors, and regenerative medicine are based on the drug’s or agent’s pharmacology, potentially including individual genetic variations, knowledge of which can contribute to targeted therapy. Such variations and targeted therapy are coming to be better understood in the current era of “precision medicine.”[2]

Radiation injury is primarily due to depletion of stem cells in rapidly proliferating tissues, followed by changes, including fibrosis and vascular damage, in slower-responding tissues. Early work focused on organ syndromes - hematological, gastrointestinal, dermatological, cardiovascular, and neurological - based on the radiation dose received. Now, we are learning that even at the lower doses some changes occur in virtually all organs, including in elements and processes common to the various organ systems. Current studies involve vascular, endothelial, and coagulation changes, and the role of acute and chronic inflammation.[3]

Mechanisms of radiation injury

For the research arm of the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), as funded by the National Institute of Allergy and Infectious Diseases (NIAID), a part of the National Institutes of Health (NIH), a primary goal of the Radiation and Nuclear Countermeasures Program (RNCP)[4] is to provide funding for foundational studies that provide the critical scientific basis that is required to seek regulatory approval from the U.S. Food and Drug Administration (FDA) for a radiation MCM. For approval of an MCM via the FDA's Animal Rule pathway, a component of the application must be a "reasonably well-understood pathophysiological mechanism of the toxicity of the substance (e.g., radiation) and its prevention or substantial reduction by the product."[5] Therefore, an understanding of how radiation exposure causes injuries is critical, as is how MCMs to treat those injuries act on the damage pathway. Much of this early discovery centers on (a) identification of biomarkers for injury, which can indicate pathways that can be targeted by a treatment; (b) demonstration of efficacy of the MCM; and (c) prediction of who may experience injuries that might arise both immediately and also following a latency period (up to months or years) after the radiation exposure. Because NIAID's mission is to fund the basic studies through translational and advanced development, it supports a broad range of studies in the hopes that the generation of efficacy data will enable MCM products to transition to the Biomedical Advanced Research and Development Authority (BARDA) for advanced development activities. Biodosimetry is included in the scope of MCMs considered for radiation exposure. In addition, when issues arise that require additional study researchers can seek supplemental funding, providing important flexibility for additional investigation and continuing, revising, or, with a significant new finding, re-starting the cycle of development that could lead to improved products (including diagnostics).

To advance drugs as treatments for radiation injury, development of animal models that recapitulate the expected injury in humans is critical. For this reason, both small- and large-animal-model development has long been a focus of the overall program.[6, 7] Important research activities that have been funded by the RNCP have included the development of mouse and rat models of radiation injury, as well as large-animal models, including dog, minipig, and nonhuman primate. In each of these models, injuries studied have included hematopoietic myelosuppression, gastrointestinal injury, and late organ complications such as pneumonitis, pulmonary fibrosis, and kidney damage.

To optimize allocation of the limited funding that is available for this research mission, the RNCP has solicited expert opinions from the research community regarding areas of science that are mature enough to benefit from targeted funding. Such areas may include animal models sufficiently advanced for use to test candidate MCMs for the various organ systems affected by radiation exposure. To that end, the RNCP has hosted over a dozen scientific workshops since 2005, many of which have generated peer-reviewed meeting reports.[3, 8-14] The diverse topics have included radionuclide decorporation agents, animal models for injury, approaches to treat lung injuries, and regeneration of platelets after radiation exposure. Identification of scientific gaps during these meetings led the way for funding opportunities in several key scientific areas, from early discovery and mechanism-of-action studies of radiation injury to advanced development to accelerate approval of MCMs with strong efficacy data.

In keeping with the NIAID mission to support early research and development, mechanism-of-action studies have identified potential biomarkers of radiation injury and amelioration of that injury by an MCM that encompass a wide range of biological responses. Biomarkers include cytokine and growth factors that change in the blood and susceptible tissues, as well as proteins and genes exhibiting expression modifications. In addition, metabolomics and other "omics" (e.g., lipid alterations, micro-RNA level changes) can be investigated on easily accessible fluids or tissue such as urine, saliva, or blood from finger-sticks, and these markers may be able to be used to predict late effects such as lung injuries and other dysfunctional/disease states.

Biological and chemical threats

While the focus on outlining CMOSSE in this article is for addressing radiation injury, the biological and chemical threats require specialized expertise of other types. Biological threats include natural outbreaks such as seasonal influenza, periodic pandemics, and infections that spread as a result of global trade and changing climate. With new gene-editing technology, concern for attacks with biologically modified organisms is high. MCMs for biological agents include vaccines, agent-specific treatments, and general management of systemic inflammatory response. For chemical agents, countermeasures and medical management are targeted to specific types of chemical threats.

In the last 15 years, the U.S. has suffered or witnessed the effects of deliberate biological attacks such as the release of anthrax in 2001, as well as the spread of naturally occurring infectious diseases like severe acute respiratory syndrome (SARS), the 2009 H1N1 influenza pandemic, Middle East respiratory syndrome coronavirus (MERS-CoV), the Ebola virus outbreak in West Africa, and most recently the Zika virus outbreak in the Americas, among others. A critical capability for responding to these types of emergencies is the rapid access to MCMs that can help avoid the spread of disease and/or reduce morbidity and mortality. To this end, the U.S. government has dedicated concerted activities through the PHEMCE, which was launched in 2006, to enhance MCM-associated preparedness for response to CBRN incidents and emerging infectious diseases (EIDs).

As illustrated in Figure 2 in the paper, the Office of the Assistant Secretary for Preparedness and Response (ASPR) leads the PHEMCE in close collaboration with the Centers for Disease Control and Prevention (CDC), the FDA, and the NIH, as well as other U.S. government agencies.[15] The ASPR Office of Strategy, Planning, Policy, and Requirements sets requirements and strategies for MCM development, acquisition, and deployment, and BARDA develops and acquires vaccines, therapeutics, and diagnostics for CBRN threats. As part of its mission, BARDA manages Project BioShield,[16] which had an initial appropriation of $5.6 billion (2004–2013), to accelerate the research, development, and acquisition of MCMs for the Strategic National Stockpile (SNS).[17] These activities included MCMs for biological threats, such as anthrax vaccine and therapeutics, a novel smallpox vaccine, an antiviral drug, botulinum antitoxin, and antibiotics for a variety of bacterial threat agents.[18] In addition, BARDA leads the advanced development and acquisition of medical and non-pharmaceutical countermeasures for pandemic influenza, including vaccines, therapeutics, diagnostics, and, in collaboration with the SNS, personal protective equipment and ventilators. Through these activities, BARDA stockpiled pre-pandemic influenza H5N1 vaccine, H7N9 vaccine, and antiviral agents, and built domestic manufacturing infrastructure for these commodities using innovative approaches to develop cell-based vaccines, antigen-sparing adjuvanted vaccines, and next-generation recombinant vaccines. BARDA also collaborates with CDC to develop point-of-care diagnostics for influenza and diseases like Zika virus disease,[19] among others.

Many countries, unlike the U.S., lack similar MCM programs and stockpiles, which limits the availability and access to these commodities worldwide. As seen during outbreaks of H1N1, Ebola virus disease, MERS, and Zika virus disease, the global capacity to respond to public health emergencies using MCMs is limited. Because of this limited supply and the lack of commercially available products, the U.S. has supported several international activities to develop or supply these products: (a) partnership with the Global Health Security Initiative (GHSI) to develop frameworks to rapidly deploy MCMs internationally to assist partner countries;[20] (b) launching of multilateral initiatives such as the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X)[21] and the Division of Research, Innovation, and Ventures (DRIVe); and (c) support for other international activities by providing subject-matter expertise, such as for the Coalition for Epidemic Preparedness Innovations (CEPI), with a mission "to stimulate and accelerate the development of vaccines against emerging infectious diseases and enable access to these vaccines for people during outbreaks."[22] In addition, the U.S. government supports the World Health Organization (WHO) activities under the WHO Research and Development Blueprint (RDB). The RDB requests proposals for "flexible development and production platform technologies … [for] vaccines, therapeutics (drugs and blood products), and diagnostics against 5 to 10 top priority pathogens/diseases, to be defined by WHO." [23] The RDB also provided critical financial and expertise support for the WHO-led Global Action Plan for Influenza Vaccines,[24] which set a "strategy to reduce the present global shortage of influenza vaccines for seasonal epidemics and pandemic influenza in all countries of the world" by increasing use of seasonal vaccine, production capacity, and acceleration of research and development (closed in 2016).

Overarching MCM considerations

Linking threats, science, and human health requires the CMOSSEs to understand what the situation may be during a response. Key aspects for the appropriate use of the MCMs are their specific indications, windows of efficacy, logistical infrastructure required (e.g., refrigeration), support needed for administration (e.g., expertise, in-patient versus out-patient, oral versus injection or infusion), and the general availability of an MCM as part of routine practice. Agents with a routine clinical use as well as use as an MCM (i.e., “dual utility”) are generally preferable in terms of availability, familiarity, and cost of provision. Diagnostics, which may include specialized tests such as biodosimetry and tissue- or agent-specific biomarkers are advantageous for initial triage and management and are discussed below. Advances in the science, particularly to enable MCMs with longer windows of efficacy, lower risks of toxicity, and greater ease of administration, could have a substantial impact on the concepts of operations (CONOPS) for how the incident is managed, as well as on effectiveness of use of the MCMs. Critical to being able to provide optimal treatment and resource utilization is rapid diagnosis, including with point-of-care assays. For example, for radiation, a valuable capability would be to categorize people for immediate discharge, for immediate need of medical care, and for further evaluation with a secondary assay. For such a capability, molecular diagnostic assays are under development. While the science is innovative and exciting, the performance of a diagnostic assay in the field is key.

Biomarkers

Triage and treatment for a nuclear or radiological incident first address trauma and obvious life-threatening injury. Supporting clinical diagnosis are laboratory studies including peripheral blood cell counts made serially post-irradiation.[25] Neutrophil, platelet, and lymphocyte counts are robust indicators of absorbed radiation dose. Increasing radiation exposure intensifies the extent and severity of neutropenia, thrombocytopenia, and leukopenia. Other tools that may be used to help medical professionals assess individuals' absorbed doses are biomarker changes in genomic expression,[26, 27] appearance of circulating micronuclei,[28] or alterations in protein levels.[29] BARDA is funding the advancement of biomarker panel assays for approval through the FDA *in vitro* diagnostics product pathway to obtain approval to market and subsequently stockpile these tests. Collectively, these methods enable using clinical signs, patient symptoms, and hematological and biomarker changes to diagnose the absorbed dose and its effects for an individual. Capacity to apply such capabilities will better inform patient management, allow more efficient use of scarce resources, improve health and psychosocial outcomes, and save lives.

Management of initial injury is guided by experts from the Radiation Injury Treatment Network (RITN),[30] a network of cancer, hematology, and bone marrow transplantation centers. RITN prepared and continually updates guidelines for care available on the Radiation Emergency Medical Management (REMM) web site (https://www.remm.nlm.gov/). Members of RITN are engaged in activities ranging from basic research of tissue injury, to improving treatment protocols to help with surge capacity, to participating in routine exercises to enhance and inform response capabilities. RITN is also discussed below in Element #4 on Response Operations.

ASPR and CDC coordination and current PHEMCE

Over the past decade, the PHEMCE has evolved to better meet its mission and goals. Through more efficient and inclusive processes, PHEMCE is better positioned to address EIDs. It has increasingly reached out to partners at state, local, tribal, and territorial public health organizations, as well as emergency management and medical and hospital preparedness communities, to inform assumptions and requirements and to ensure that stockpiled MCMs can be effectively utilized in an emergency.

Within the PHEMCE, partner agencies collectively agree on strategic priorities, as detailed in the PHEMCE Strategy and Implementation Plan (previously annual; now biennial). They contribute their individual expertise and leverage strengths across agencies to accomplish these goals. For example, as statutorily required, CDC and ASPR have jointly led the PHEMCE in an annual review of the contents of the SNS; now that the SNS has been moved into ASPR, it will have the lead in this review. This annual review by disease-specific scientific experts and policy decision-makers provides guidance for maintenance and use of limited stockpiled resources that are most needed to reduce risk across the priority threats. In the collaboration, ASPR provides its deep understanding of the current requirements and pharmaceutical pipeline, while CDC leverages its scientific expertise, relationships with public health and emergency response partners at all levels, and its logistical experience to ensure a stockpile of the right medicines and supplies that can be available when and where needed to save lives. For a nuclear or radiological incident the CDC has important expertise in radiation and health physics,[31] as well as a radiobioassay laboratory and network. Management of the SNS was transferred from CDC to the Office of the ASPR in October of 2018.

CDC's National Center for Environmental Health (NCEH), Radiation Studies Section (RSS) focuses on the public health implications for the nation of public radiation exposures and radiation-related health threats. RSS has worked extensively with other federal agencies to provide public health assessments and recommendations on a variety of radiation-related programs and topics, including historical dose reconstructions for former nuclear weapons production and testing sites, radon, MCM acquisition/stockpiling/use, nuclear power plant accident exercises, and food safety issues. CDC is a member of the Advisory Team for Environment, Food and Health,[10] which interprets data provided by other agencies to develop health-based protective action recommendations for decision makers during a radiation emergency.

RSS is the lead focal point at CDC and its mission is to protect the public's health from radiation exposures from environmental, medical, and emergency sources through science and education. RSS staff members serve as the lead technical subject matter experts (SMEs), and CDC's National Center for Environmental Health is the lead for the agency with regard to radiological incidents or any radiation-related public health issue. RSS staff members are nationally and internationally known for their expertise, serving on the National Council on Radiation Protection and Measurements (NCRP), the WHO's Guideline Development Group, the WHO's Radiation Emergency Medical Preparedness and Assistance Network, and the UN Scientific Committee on the Effects of Atomic Radiation. RSS members also collaborate and consult with the International Atomic Energy Agency, the International Criminal Police Organization (INTERPOL), and the GHSI. RSS staff members have been called on for assistance with numerous national and international emergencies including the Fukushima nuclear power plant releases in 2011, the Polonium-210 poisoning of a former Soviet agent in 2006, and national-level exercises of the National Response Framework. The RSS is recognized as a valuable resource for its preparedness materials and technical assistance in U.S. and international radiation emergency preparedness planning. This subject-matter expertise and the associated programmatic activities, as well as many of the critical partnerships, are unique to the CDC.

The RSS provides assistance and support in all radiation-related matters to state and local agencies. It does this by providing technically accurate, focus group-tested capacity-building resources, including training, education, tools, and guidance. The RSS does not have sufficient budget to provide extramural funding directly to state and local agencies for radiation emergency preparedness; however, the branch works with the grant-funding programs of the Division of State and Local Readiness and the Public Health Emergency Preparedness (PHEP) cooperative agreement within CDC to help state and local agencies optimize their PHEP funding toward preparedness goals.[32] In addition, the RSS works with key partners such as the Association of State and Territorial Health Officials (ASTHO), the National Association of County and City Health Officials (NACCHO), the Council of State and Territorial Epidemiologists (CSTE), and the Conference of Radiation Control Program Directors (CRCPD) to provide valuable resources and alliances to improve the nation’s radiation-related preparedness posture.

Element 2: Modeling and Systems Management

<u>Scientific underpinnings of analysis and data synthesis</u>

Anticipating the potential threats and what an incident will involve in terms of casualties and the need for “space, staff, and stuff”[33] requires modeling and quantitative assessment for synthesizing information from a wide range of disciplines to estimate what may happen and identify what we could do to respond. To enhance the likelihood of utility of the models, a number of groups work in collaboration and share expertise to best define the scope of the situation, even though no model can be considered to be precisely predictive, given uncertainties about what will occur (often reflected in the statement that "all models are wrong but some are useful" [George Box[34]]). The Department of Homeland Security (DHS) conducts terrorism risk assessments to identify threats of different types, how likely they are to occur, and how many people may be exposed.[35] These are classified documents. With the PHEMCE,[36] the ASPR Modeling and Simulation Branch conducts public health and medical consequence modeling, including representations of types and time courses of injuries, potential MCMs and other resources for treatment, and the space and personnel needed for response. These models are based on the best available epidemiology and computational science in the open literature, and they may also rely on classified data or other controlled, unclassified information (CUI), including "for official use only" (FOUO) and proprietary information, to define critical input assumptions and parameters, resulting in output results that are often not publicly sharable.

Modeling

Modeling, displaying the information, and being able to utilize it in real-time are constantly evolving. Not only does the information that goes into the models change, but the types of models and the technology to do the calculations, utilize it, and display the data evolve. Expertise is available from the U.S. national laboratories, the Department of Defense (DoD) and the DoD's Defense Threat Reduction Agency (DTRA), ASPR, and non-government "think tanks."

National laboratories and technical organizations

Many federally funded research and development centers (FFRDCs) sponsored by the Department of Energy (DOE) and DoD maintain a core science capability to support response planning for CBRNE incidents. Preparedness activities for complex, technical hazards require a sound scientific basis integrated into appropriate guidelines and preparedness activities.[37] Federal CBRNE response planning activities are often built on an analytical framework of supporting science developed by national laboratories and other technical organizations.[38] For several decades, researchers have helped federal emergency officials and their state and local counterparts better understand the science underlying a host of natural and human-caused disasters.[39] More recently, FFRDC scientists are working to formulate the most effective ways for responding to low-probability, high-consequence human-caused incidents involving nuclear, chemical, or biological materials. This task has become more urgent as the nation's population continues to move into dense urban centers, where great numbers of people gather in public areas such as arenas.

The greatest reduction in loss of life often comes from helping communities to better prepare for the critical minutes and hours shortly following a disaster. Researchers use advanced modeling and simulations to project that many lives can be saved during CBRNE incidents with just some key planning knowledge, even for incidents that occur without warning. Advanced simulations, shared broadly with federal, state, and local agencies nationwide, serve as excellent training tools and can form the basis for community-specific emergency response plans. Recent advances in our understanding of the hazards posed by CBRNE incidents include detailed atmospheric dispersion modeling from the advanced suite of three-dimensional meteorology and plume/fallout models, including extensive global geographical and real-time meteorological databases to support model calculations. Combining potential impact assessments with an analysis of detailed, geolocated information on population, shelter options, transportation, and infrastructure help response planners estimate the advantages and disadvantages of various courses of action.

Although sound science is the cornerstone of good response planning, it must be tempered with operational realities and strategies. Although planning for a potential CBRNE incident is not a pleasant task, researchers are showing that when planning is based on science and advanced modeling, the payoff could be great numbers – in some cases tens of thousands – of lives saved.

Key to the concept of CBRNE science is that modeling, quantitative assessment, and synthesis and visualization of information for decision-making involve exploration of questions that are fundamentally interdisciplinary, requiring groups of analysts with diverse backgrounds. Being quantitative, modeling teams require members with a good understanding of math and statistics to ensure that inputs are sound and outputs are meaningful. Members of this cross-disciplinary team require expertise in computer programming and the use and development of software platforms to produce robust models and visualization tools that can provide results fast enough to be relevant to answer the questions posed. However, perhaps the most important requirement is to have team members that understand the science underlying each of the specific hazards and the associated medical and public health consequences on the impacted population. Additionally, because their analyses often use controlled and/or classified information, many CBRNE scientists will require a security clearance, and some or all results of the analyses may not be able to be published in the open literature.

Modeling, quantitative assessment, and clear visualization of complicated information are essential to synthesize a wide variety of data both for preparedness and in real-time responses to threats of any type (all-hazard). This component of CBRNE science informs key decisions for health emergencies across the spectrum of natural and human-caused hazards. Models enable the exploration of the complex interplay among the hazard, the response, and outcomes. This toolset is drawn from a wide array of fields, including computational science, epidemiology, applied mathematics, statistics, economics, management science, operations research, and industrial engineering, to name a few, and leverages different methodologies and platforms depending on the particular question of preparedness being addressed. Agent-based models are often used when the behavior of individual people matter and the differences in personal choices can influence public health outcomes. For example, an agent-based model has been used to determine which approaches to triage would save the most lives after a nuclear detonation yet preserve the principles of fairness and equity in the medical system.[40] In this model, surgical teams were the agents, various triage priorities were modeled, and the total lives saved were compared using various triage rules. Agent-based models are also often used when modeling the course of a transmissible illness through a population, especially when assessing how individual level decisions could impact transmission dynamics. Population-based models are useful when the behavior of members of a group of people could be expected to be roughly uniform if they are treated in the same way. For example, a population-based, Markov-chain model could be used to describe how various strategies for prophylaxis and treatment would reduce the casualties and deaths resulting from a release of anthrax spores in a city. Similarly, a population-level SEIR-type (Susceptible – Exposed – Infectious – Recovered) compartment model can be used to explore how different types and efficacies of mitigations might impact a pandemic influenza outbreak.[41] Given that resources to support preparedness activities are limited, coordination of modeling, simulation, and acquisition enables a consistent framework for trade-off analysis to guide investments. The development and use of high-quality models, analyses, and effective data visualization and communication tools are ongoing activities, not only because the information that goes into these analyses changes, but also because the types of models and underlying technology to do the calculations and display and utilize the data are constantly evolving.

Analysis and data synthesis for preparedness

Modeling and quantitative assessment is informed by, and can inform, every aspect of the preparedness enterprise. Within the government and in non-governmental think tank settings, every effort is made to direct this type of analytic resource to answer key questions posed by preparedness stakeholders. However, these types of analyses cannot be conducted in a vacuum, as models are useful only if they simulate how a system will actually behave under real stresses. For this reason, models need data from clinical and basic research on how hazards imperil human health and how the application of MCMs and other resources improve health outcomes of victims. Likewise, data are needed from the planning community and the stewards of strategic resources regarding the type and amount of resources needed to best implement the response. Conversely, models can identify where scientific uncertainty undermines thoughtful preparedness and thereby what additional research is needed. For example, synthesis of modeling estimates of population movement after an improvised nuclear device detonation with animal model and human clinical data on cytokine treatment identifies new avenues for basic and clinical research to identify how effective these treatments might be when people make it to definitive care. Results of modeling assessments could also be used to inform how much diagnostic capacity for each threat is needed to best reduce risk and which diagnostics should be prioritized for funding. In a study of more than 100 chemical, biological, or radiological agents, we found that a novel diagnostic would improve the health outcomes in the aftermath of attacks with only a handful of agents because others produce illness (a) that is easy to diagnose (e.g., acetylcholinesterase inhibitors), (b) that is effectively treated even when misdiagnosed (e.g., *Francisella tularensis*), or (c) cannot be effectively treated or mitigated even if diagnosis is accurate (e.g., ricin).

At the tactical level, modeling, quantitative assessment, and synthesis and visualization of information support decision-making throughout the preparedness spectrum. For example, modeling is used in the federal government to identify injury types and which types of MCMs are needed, which guides clinical and basic research and development activities toward new MCMs, sensors, or medical systems that could best improve preparedness.[42, 43] At the most tactical level, information on the amount of a particular resource (e.g., vaccines, treatments, personnel) needed and available, including gaps between need and availability, can inform cost-effectiveness of options to further mitigate risk of any particular threat or to best mitigate negative effects associated with any plausible scenario. When modeling uncovers critical vulnerabilities or new threats, for example the potential overwhelming need for critical care ventilation therapy during a severe pandemic influenza outbreak, CONOPS and associated plans can be adjusted to minimize the preparedness gap until technological advancements can address the shortfall.[44] Additionally, modeling can be used to determine if particular injuries or special populations should be prioritized to receive scarce resources to reduce the overall health consequences of an incident and inform the requirements for the timing and extent of a response. For example, in preparing for the recent Zika virus outbreak in Puerto Rico, modeling, simulation, and quantitative assessment were essential to identify the potential amount of treatment resources that could be required for the small fraction of infections associated with Guillain-Barré Syndrome. Finally, when local, state, and federal preparedness budgets are decreasing, modeling can be used to inform priorities on resource allocation for various scenarios and which cuts would be most likely to have the least detriment to preparedness.

Given that human health is imperiled by a variety of threats that could strike many locations in the U.S. (or the entire U.S.) and cause consequences ranging from a handful of illnesses to millions of deaths, modeling, quantitative assessment, and information synthesis and visualization can be used to assess the complexity of the threat landscape and the ability of resources to mitigate risk. GeoHEALTH is a flexible platform developed and maintained by the ASPR Office of Incident Command and Control that allows the visualization of data from inside DHHS as well as data that are available from external sources such as weather data from the National Oceanic and Atmospheric Administration (NOAA) and data from the United States Geological Survey (USGS). Data loaded into the GeoHEALTH database is assigned one to many roles determining who may access the data,[45] allowing for users with the matching role to access this data and view it along with any other data layers to which they have access. Many tools and specialty applications are available within the GeoHEALTH platform allowing users to collect, record, and manipulate the data, to explore the data, and additional possibilities based on the user's needs and developing situations. The platform empowers users to interact with the evolving data in ways they determine; it is not confined to predetermined methods of display.

At the strategic level, modeling, quantitative assessment, and synthesis and visualization of information help describe the relative risk posed by a variety of threats and the ability of preparedness activities to mitigate those risks, thereby guiding the allocation of resources overall. For example, should resources be spent stockpiling vaccines for a single disease or for better medical surveillance to help identify a variety of health threats before they become major problems (but only partially mitigate those threats)? Looking ahead, while these activities already inform many aspects of preparedness, they could play a much larger role. Across the government, funding levels for various programs could be informed by a sweeping, strategic model that assesses the threat posed by “all hazards” including natural, accidental, and intentional threats, and evaluates the ability of every program, platform, and office to mitigate the threat overall. Trade-offs between model complexity, speed, and flexibility would be essential to allow a system like this to rapidly be adapted to incorporate new threats or new capabilities. Similarly, relatively simple and purpose-built models of the performance of the healthcare system are often used when examining questions of medical preparedness. However, because of the limited resources invested, these models often use simplifying assumptions about medical transport of injured to hospitals, triage, staffing, space, and supplies, including the interplay among these elements. For example, models often do not consider how critical medical personnel and/or supplies could substitute for one another, and how hierarchies influence scarcity and effectiveness of medical supplies. Can antibiotics be administered if nurses are scarce or no IV administration supplies are available? If anti-emetics are scarce, can oral antibiotics be administered? Should anti-neutropenics be administered if antibiotics are scarce? Omission of such considerations is often due to the reluctance of SMEs in a medical response to explicitly and quantitatively address tradeoffs like these before an incident, leaving such considerations to post-hoc studies. A strategic investment in the collection of this type of crisis-standard-of-care data to inform development of a robust model of the healthcare system under stress that is open-source and flexible enough to be used in the face of a variety of threats would enable CBRNE preparedness activities to more accurately reflect important realities in the medical response to an incident, provide policy-makers with more robust guidance and, possibly, operate in real-time during an incident to guide the allocation and distribution of resources. To address this, national CONOPS will be developed (discussed below).

Analysis and data synthesis supporting response

Modeling, quantitative assessment, information synthesis, and visualization can be considered critical components of decision-making during a CBRNE incident. During an incident, for example, the Interagency Modeling and Atmospheric Assessment Center (IMAAC) would provide information on weather, as noted in the main paper.[46] Additionally, tools like GeoHEALTH [45] enable users to synthesize data from many sources and to view many layers of data at the same time to provide a more realistic view of what is happening in the real world and to plan accordingly.

When ground-truth data are scarce and applicable models do not already exist, an embedded cross-functional team of talented analysts is essential to conduct rapid analyses to inform real-time decisions to guide the allocation and distribution of resources including detailed information at the community and regional levels. For example, during the 2014-2015 response to the West African Ebola outbreak a multiagency team of analysts developed tools to estimate the potential needs for specialized Ebola treatment beds in the U.S.[47] Many of the decisions made during a response rely on accurate estimates of the magnitude and timing of potential impact. During the West African Ebola outbreak, government, academic, and non-governmental groups developed models to synthesize disparate information and incomplete data to forecast potential cases over time. The results of these analyses were essential to guiding a wide range of U.S. and international decisions on response actions. After the operational tempo of the response slowed, the Research And Policy in Infectious Disease Dynamics (RAPIDD) program led by the Fogarty International Center of the National Institutes of Health (NIH) conducted an Ebola forecasting challenge to evaluate the accuracy of the types of models used during the response with multiple synthetic outbreak scenarios, including a variant of the model that guided ASPR's real-time decision-making during the response.[48-51]

While current response support often relies on in-house analysts to develop new models and complete quantitative assessments in real time, an area under active development is the ability to use the preparedness models as tools to plan for and also guide response in real-time, a concept called "national CONOPS." In large-scale incidents, the entire nation and even international neighbors and partners will be involved. Being able to plan and respond in a coordinated way will optimize the use of personnel and resources beyond the local area, accounting for the diaspora of people from the incident, as occurred following Hurricane Katrina.[52]

Modeling, quantitative assessment, and synthesis and visualization of information can support the development of national CONOPS in a variety of ways. For example, cross-threat synthesis of quantitative assessments and models can identify which aspects of national CONOPS can be leveraged to address cross-threat needs and prioritized to have the greatest potential to reduce negative consequences of a CBRNE incident. While mass prophylaxis may be useful for the response to some biological attacks, it may have limited utility in most other scenarios. However, national CONOPS for patient movement and maximizing hospital surge capacity have utility in nearly all large CBRNE scenarios. Additionally, a flexible national CONOPS capability can provide a platform to test and evaluate competing response options ahead of time, and synthesize real-time information feeds to assess implications of potential resource deployment options that otherwise meet all operational requirements. A critical need and gap is the importance of *modeling community-level approaches* as well, that is, the relative investments of resources vs. return in terms of potential lives saved.

Element 3: Planning

Taking the concepts behind preparedness and transforming them into detailed step-by-step plans is critical, requiring effective collaboration among the various agencies and responsible authorities that will provide the resources. Plans have both generic components and "threat-specific" details that are organized in a time-oriented and sector-dependent manner. These steps are organized in playbooks. Each agency has its own set of playbooks that are not publicly available. To assist in collaboration and coordination, ASPR developed a *State & Local Planners Playbook for Medical Response to a Nuclear Detonation*.[53] Initially, separate playbooks were developed for each of the national planning scenarios.[54] Given that the scenarios have many aspects in common, an all-hazards playbook is in development by the Office of the ASPR and the National Library of Medicine (NLM), Specialized Information Services.

All-hazards approach

All-hazards planning requires recognition that, regardless of the cause of a disaster, households, businesses, and community organizations must respond in roughly similar ways. This is not done by compartmentalizing various disaster agents and addressing each separately. Rather, the approach is to begin first by assessing what various incidents have in common with respect to response demands, and only later focusing on contingencies specific to the different threats. For example, responsibility for management, direction, and control must be assumed no matter what type of disaster agent is involved. Additionally, sheltering, feeding, and providing healthcare services to victims, restoring essential services, overcoming transportation system disruption, and removing debris are critical regardless of the type of disaster. Addressing the need for appropriate and sufficient resources is a generic preparedness task, even though specific resources needed to deal with different types of disasters vary.

In cases in which hazard agents require distinctly different responses, hazard-specific planning, training, and resources are required. The contents of hazard-specific annexes focus on the special planning needs. These annexes contain unique and regulatory response details that apply to a single hazard. Hazard- or incident-specific plan annexes can identify hazard-specific risk areas and evacuation routes, specify provisions and protocols for warning the public and disseminating emergency information, and specify the types of protective equipment and detection devices needed for responders.

Requirements

Development and acquisition of any product is best done in light of requirements specifying the characteristics of the product. Generally, "products" for preparedness include supplies to be used in response, and planning or communication products (e.g., plans, CONOPS, guidance, messaging) for guiding the response. Planning is typically based on scenarios to frame the needs, considering potential incidents and the capabilities required to meet them. This entire publication can be seen, in a way, as including a framework for high-level requirements for planning and communication products. This section, therefore, focuses on requirements for supplies that will be needed in a response, with MCMs in mind as the most critical type of supply, with consideration of challenging features for effective development for response.

Requirements include: (a) qualitative information on the inherent characteristics of supplies to be developed and ultimately acquired, which may include physical features, medical effects, use characteristics, and regulatory considerations, and (b) quantitative information on how much would need to be available. Both types of information depend on the scenario(s) being addressed. Therefore, scenario-based analyses, assessing needed capabilities, are important inputs to more specific requirements for supplies, and are a standard part of the requirements process for MCMs. Requirements for inherent characteristics depend on the medical or response need being addressed, considering the applicable scenario(s). The amount is assessed in light of: (a) the quantitative need associated with the scenario(s), (b) plans for how the supplies would be made available, and (c) capabilities for using the supplies. Plans for availability and capabilities for use, in turn, depend on various parameters including the time course of the need; the type of supplies and how and by whom they can or must be used; and whether such supplies are used in conventional care or commerce versus being specialized for emergency response scenarios. For example, depending on the time course of the need for the supplies, availability might be feasible from a central stockpile or might need to be locally, quickly available (or both).

Part of the development of scenario-based analyses is to determine the full range of types of MCMs needed to respond to a given type of incident. If gaps exist in availability of existing MCMs, this can be addressed based on the needs determined from the scenario-based analyses.

Because of operational and life-cycle-cost advantages, an emphasis has recently been placed on "dual utility" supplies, which are used in conventional care or commerce, but also have emergency response applicability. However, some emergency needs may not currently be able to be met with such products, while specialized emergency-specific products may exist. For "emergency-only" type products, cost is an especially critical factor in decisions on acquisition, as when they reach the eventual expiration date they must be discarded and replaced, even if not used, after all means of extending expiry dating have been implemented.

The depth of detail needed for modeling here is an extension of what was presented above in Element 2: Modeling and Systems Management. In general, modeling of the benefits and costs of various types of products and means of supply informs decisions on requirements, importantly including estimates of population health consequences (mortality, morbidity) for the candidate methods, as well as features affecting life-cycle costs. In many cases, information needed for fully informed modeling is not available. Therefore, assumptions are made to provide the best projections. Caveats are associated with the uncertainty regarding the validity of the assumptions, and range-determining excursions can be used to explore effects of variations on the assumptions. Nevertheless, with applicable caveats and excursions, such modeling can usefully help frame decisions with informed projections. The CMOSSE and SMEs are critical in recommending key areas of research and development to fill gaps.

A challenging feature of developing requirements for supplies is interdependence among: (a) characteristics of the supplies, (b) the ways in which the supplies can be used, (c) the maximum amount or rate at which the supplies can be used, (d) the amount of supplies to be provided, and (e) the cost of the supplies (fundamental product requirements may not address costs, which can be factored in at later stages of acquisition decisions, with acquisition-specific requirements and consideration of trade-offs with other potential uses of the funding). Variation in one of these parameters can affect the requirements for another of them; this is an example of the complex systems required to be understood by the CMOSSE. For example, if a product has substantial constraints in how it can be used, such as needing high levels of expertise to administer (e.g., IV drugs), use of large amounts in limited time may not be operationally feasible given the numbers of people available with the relevant expertise, and therefore the quantity required may be limited to an amount projected to be operationally feasible to use. An important part of ascertaining quantitative requirements for products, therefore, is estimating the maximum quantity operationally usable. This "operational quantity" is a main subject of capabilities-based assessments.

Estimating an operational quantity is particularly challenging, given the dependence on many factors that are hard to predict for a given type of scenario and that vary with the location in which an incident may occur. Useful estimates must be both realistic and aspirational. They must be realistic because if we substantially overestimate we risk gratuitously spending valuable resources on supplies we could never use (even if needed). They must be aspirational because if we underestimate we risk gratuitously losing lives or health we could have saved if we had a full complement of supplies we could use. Improvements in the product and CONOPS go hand-in-hand to improve the effectiveness of a response.

Subsequently, an assessment of gaps in preparedness can afford an opportunity to determine what initiatives are needed to close the gaps, and such initiatives can be prioritized based on assessments of potential benefits and costs. The PHEMCE has used a process of preparedness assessments for use of established MCMs or types of MCMs, in which preparedness is assessed in five categories: (1) research and development; (2) manufacturing capability; (3) procurement and stockpiling; (4) response planning and guidance; and (5) operational capacity. The fifth category is equivalent to the operational quantity noted above. When gaps are revealed by this process, initiatives are developed to address them.

Scarce-resources setting

Perhaps the most challenging aspect of medical care during a large-scale disaster that distinguishes it from "business as usual" is that sufficient resources may not be available for all who need them. This is called a scarce-resources situation. Preparing for this includes determining the resources and guidelines for medical triage. This involves ethical considerations and algorithms and guidance for fairness.

Large-scale incidents, by their very nature, require decisions regarding the allocation of public health and medical resources. Depending on the incident, shortages may occur of specific types of resources such as ventilators; or enough resources may exist, but they may not be located near to where they are needed; or resources may be insufficient more generally. Starting in 2007, the ASPR began working with different organizations to convene experts to develop the science of scarce-resource allocation. Following initial work with the Agency for Healthcare Research and Quality,[55] ASPR commissioned the Institute of Medicine (IOM; now the National Academy of Sciences, Engineering, and Medicine) to develop a national framework for the allocation of scarce resources. The IOM committee issued a letter report [56] and several subsequent reports describing the concept of crisis standards of care and providing specific guidance on implementation. These subsequent reports included guidance on engaging the community to help define the underlying values that should guide resource allocation decisions [57] and specific indicators and triggers for the implementation of crisis standards of care.[58]

In 2012 the IOM committee defined a "systems approach to disaster planning and response." [59] In that report they maintain that such a systems approach is needed to "integrate all of the values and response capabilities necessary to achieve the best outcomes for the community as a whole." The two foundational cornerstones of the framework are ethical considerations and legal authorities. In a subsequent manuscript the practical challenges of implementing a systems approach are described.[60] At the heart of planning for crisis standards of care is ensuring that the decision-making process reflects the ethical values and priorities of the community. To achieve this, planners must engage the community in a conversation about how to deliver care in scarce-resource situations. The IOM committee developed a tool kit to assist planners with this type of community engagement.[58] Some states have implemented this type of community engagement to inform their planning activities.[61]

While the focus of decision-making for the allocation of scarce resources is at the local level, equally important is for decision-makers at the federal level to apply an ethical framework to the decisions about the allocation of federal resources when requests for assistance exceed the available resources. Using a deliberative process that involved input from disaster experts and ethicists a framework for the allocation of scarce federal resources was proposed.[62, 63] A conceptual framework for allocation of the ventilators that are in the SNS has been proposed.[64]

Using the above principles, a working group addressing scarce resources for a nuclear detonation developed the background information and triage guidance in a series of papers.[40] A key issue of fairness is the need for community and responder preparedness in advance of the triage system and what determines when the triage order changes as a result of changes in the austerity of conditions, from normal to good to fair to poor. This determination is particularly critical for a huge, no-notice incident such as a nuclear detonation. To assist in this endeavor, particularly if no preparation is completed in advance, REMM contains a triage guidance, algorithms, and a tool (https://www.remm.nlm.gov/). Addressing shortages involves all aspects of the problem – supply, demand, operational capability, substitution of resources, and others.

Supply chain

If the key tenet of health and medical preparedness, planning, and response is to have the best science underpin the strategy, specific functions, and tasks, then a necessary component to support this tenet is to have a timely, efficient, and effective supply chain capable of responding when and where needed with the right MCMs, in the quantities needed. Under ordinary circumstances, for most providers and patients, this is a transparent process, requiring little thought when things are on the shelf. However, when extraordinary incidents disrupt the continuity of health care, paying attention and having some appreciation of supply processes is necessary for the most effective response. From a supply perspective, three elements contribute to preparedness and response:

1. Supply planning begins at the product level and continues at every facet of the supply chain. That is, planning is important for a drug, biological agent, or device as it evolves through the early phases of its product-development lifecycle to pre-market approval, use in the marketplace, and finally ending with its discontinuance and removal from the marketplace. Conducting supply-chain planning is (a) the role of the product-development team as it establishes specifications for how the product is envisioned to be produced, supplied, stored, packaged, and handled, and (b) the role of supply-chain partners (i.e., the collective organizations, systems, activities, and resources engaged in product manufacturing and shipment activities, from manufacturers to distributors, for ultimate receipt and use by healthcare providers and patients).

2. Risk assessments and mitigation activities are important across the supply chain to ensure all elements are resistant or resilient to disruptive changes in the supply chain (a) by implementing mitigating strategies to ensure continuity of supply, and (b) by implementing measures that ensure the security and safety of products, such as qualifying suppliers and entering into distribution agreements with distributors that make it harder for counterfeit or adulterated products to enter the market.

3. Coordination is important with federal, state, and local officials as partners in all-hazards response-and-recovery planning. The National Incident Management System (NIMS) is intended to be used by the whole community. Since much of the support that facilitates

response and recovery comes from the private sector, the organizations comprising the supply chain are integral components of that process. To that end, supply chain partners and their industry associations are encouraged to collaborate with federal, state, and local officials such as those in the Federal Emergency Management Agency's (FEMA) National Business Emergency Operations Center, ASPR's Health and Public Health Sector Critical Infrastructure Program Office, and the SNS.

Preparedness and response at the national/international interface – globalizing activities

In an increasingly interconnected world, the spread of infectious diseases with pandemic potential or the deliberate or accidental use, release, or detonation of CBRNE agents can easily develop into public health emergencies that can impact not only the health security of the U.S., but also global health security. An infectious disease outbreak or a CBRNE incident may pose a risk to widespread populations, potentially globally. Managing and coordinating preparedness and response to these emergencies increasingly requires simultaneous domestic and international actions that need to be interrelated for a timely, efficient solution. Our country has recognized this interconnectedness through the National Health Security Strategy (NHSS), the Global Health Security Agenda (GHSA), the GHSI, the North American Plan for Animal and Pandemic Influenza (NAPAPI), and a variety of policies and initiatives that focus on the CBRNE science concept to enhance international collaborations around it to prepare our region and the world. These initiatives bring together SMEs from the U.S. in close collaborations with world-wide policy and technical SMEs to implement the CBRNE science cycle. For example, through this work, our experts hold workshops on the latest scientific and medical advances on CBRNE and EID knowledge; develop tools for threat and risk assessment and early alerting and reporting of threat incidents; and develop plans for various purposes, such as: (a) international emergency communications; (b) other public communications; (c) international deployment of MCMs and biological samples key to developing diagnostics; (d) international deployment of medical and public health personnel; (e) decontamination after radiological and chemical incidents; and (f) laboratory surge capacity. Through GHSA for example, we have been able to advocate and support a systematic approach to build capacities to respond to biological threat agents and to develop a process for countries to assess their own preparedness and response capacities for all hazards through a joint external evaluation process that uses world-wide agreed-upon metrics under the framework of the International Health Regulations (IHRs).[65] Through the NAPAPI, the U.S. is working with Mexico and Canada to develop policies for regional preparedness for influenza pandemics. This work brings the health, agriculture, security, and foreign affairs sectors to share scientific advances in the field, and to operationalize mutual assistance protocols, to ensure rapid response and recovery from disease outbreaks with pandemic potential. In addition, the U.S. fully supports the role of the WHO under the new Health Emergencies Programme, which is "designed to address all hazards, flexibly, rapidly," to address "the full cycle of health emergency preparedness, response and recovery in support of local community and national government efforts."[66]

These are just a few examples of the activities that the U.S. has undertaken to develop a national/international preparedness interface, to align scientific research programs and policies, and to build programs and plans to ensure that our country and other countries' and organizations' systems are adequate and interconnected to allow for coordinated responses to global threats.

Communications

Communications require extensive preparation and expertise. The obvious fear from disasters and pandemics and the highly complex nature of the illnesses and science require close working relationships with SMEs and communications experts. Messages are prepared in advance,[67] reviewed with focus groups, and standardized to the extent possible to avoid ambiguity and confusion. Expertise in utilizing social media is essential. To enhance clarity and effectiveness of communications during an incident CMOSSEs must work closely with communications people, including participation with the presentations and question and answer sessions with the media.

The experiences of 9/11, Hurricane Sandy, Fukushima, and the H1N1, Ebola, and H7N9 outbreaks have demonstrated that public communications is a critical component in the planning for, response to, and recovery from any public health emergency. With the need for immediate and sustained action from responders and the public and with the lack of public understanding of CBRN agents, effective communication will be an essential element of saving lives during CBRNE response.

The field of crisis and emergency risk communications has evolved significantly since 2001. Through an iterative process, it has become an accepted set of principles on which public information is built before, during, and after a crisis.[68] Risk communications literature shows that concern and outrage grow exponentially when the affected public has no control in its exposure to a risk, particularly to a human-caused threat. A CBRNE incident is such a risk. In a crisis, the information source or messenger and the mode of communications delivery matter as much as the message itself in fostering the trust necessary to persuade the public to take appropriate action and to avoid inappropriate action. Thus, incorporation of risk communication and its principles is crucial in medical emergency response to a CBRNE incident.

For radiological and nuclear incidents, messaging by SMEs familiar with radiation injury and risk is particularly critical, as exemplified by experience in Japan during the response to the Fukushima Daiichi Nuclear Power Plant crisis. The importance of a meeting to discuss the issues with the general public, such as a town hall meeting, cannot be overemphasized. Relevant today is the need for messaging and preparation with the expanding risk of nuclear confrontation.

Element 4: Response and Incident Management

Response

CBRNE science is about aiming to have the "perfect" response. Essential components to response begin with planning and require close collaboration among the state, local, tribal, and territorial authorities and the federal agencies. While the federal government has an important convening role, much of the scientific expertise and real-world experience in CBRNE science are in the private sectors, so that their involvement is integral to planning and response.

Operations

As noted in the main paper, an ongoing interaction between the Emergency Operations Center and CMOSSE will not only enhance an ongoing response but will also lead to new approaches as experience and ideas are exchanged. Routine interaction also develops a level of trust, comfort, and confidence in what the various team members provide.

Each disaster response has its own characteristics, focus, priorities, and 'aha' moments. The general face of medical response to disasters changes dramatically over time and medical disaster response managers are constantly building our toolbox based on the ever-deepening experiences of the latest issues that we have faced.

The number, frequency, and complexity of disasters, including new and reemerging infectious diseases, has been increasing in recent years.[69-71] Many years ago, the primary focus of large-scale medical disaster response was on hospitals. As medical disaster managers triaged their activities and resources, some of the out-of-the-mainstream health and medical needs may not have received all the attention they deserved because the larger issues consumed the bulk of available support. Only when hospitals and healthcare systems' disaster preparedness became more robust and resilient – through a combination of regulation, preparedness grants, adoption of best practices, and individual activities – could the available disaster medical response activities and resources be dedicated to some of the needs on the periphery of the healthcare continuum.

Consequently, the evolution of medical disaster response is growing from one that focuses on strictly disaster medicine toward a more encompassing holistic approach that includes more disciplines and social and environmental components.[72] As such, the practice of disaster management must likewise continue to expand to incorporate more specialties and access an ever-increasing body of knowledge. In practice, this requires three main initiatives. The first is to develop a continuous-process-improvement culture in which participants review all operations, seek out opportunities for improvement, and revise practices to incorporate improvements. This process of self-examination reveals additional requirements that tend to expand into more peripheral aspects of the total needs of a disaster response. The second initiative is to build a cadre of experts that can contribute their much-needed knowledge and experience to help shape the response plans and activities. A wide variety of disciplines must be represented to provide a more comprehensive response. The third initiative is to improve information management to share more relevant information with a larger audience so that they can understand the totality of the operation.

Continuous improvement

An effective continuous improvement program for disaster response should include timely after-action review of issues and opportunities after each operation and exercise.[73-75] Three examples follow of how best to accomplish this. One is to have designated individuals query response and incident management personnel during the response or exercise. They can collect real-time feedback that can be used both to address issues during the operation and to record them for process-improvement actions after the response or exercise. A second practice is to bring responders and incident management personnel together before they demobilize, for a "hot wash" review of the activities that were just completed. Collection of response feedback either immediately or very shortly after a response is important in gathering accurate information.[76] A third method is to gather semi-anonymous comments into an automated system during or after the operation. Semi-anonymous means that contributors' identities would not be published, but the managers of the corrective action process would know who they are, so they could reach out for clarifications. Fully anonymous comments, with no ability to contact the submitter, carry the risk of being misinterpreted. All three of these processes can be used to capture as many issues or opportunities as possible. The collected feedback must then go through a process in which the issues are examined, potential solutions are researched and vetted, and process changes are implemented and evaluated for effectiveness.

Cadre of experts

To say that most large-scale disasters are complex would be an understatement. For example, in contrast to a house fire that may have relatively few factors affecting the complexity of response, large disasters may require considerations for numerous complicating factors. To manage the complexity of large-scale medical disaster responses, a cadre of SMEs that can be drawn upon as needed is a prudent resource. The expertise of the cadre should be as wide as the continuum of health care. A whole host of other experts should be available to the disaster management team to support areas such as these:[70, 77]

- Hazardous materials (HAZMAT)
- Individual medical and human services needs for all sectors of the population
- Animal needs (pets, companion animals, working animals for law enforcement and rescue teams, and livestock)
- Communication to all the population including those with barriers associated with technology, language, or other communication issues
- Social factors
- Legal issues
- Consideration for long-term recovery
- Law enforcement
- Environmental impact
- Political issues

A desirable strategy is to build a cadre of experts in a variety of areas during 'peacetime' so that they can be called in for support during response.[71, 74, 78, 79] Experts can be from the fields of industry, academia, government, professional organizations, or other sources. These experts can provide real-time advice and information to support decision-making. In many cases, the members of the cadre may also have networks of experts from whom they can draw additional information. Developing and managing a cadre of experts is an effective means to address the numerous complexities of large-scale disasters in today's environment.

Information management

Information management is a factor that weighs heavily in the complexity of large-scale medical disaster response. Many entities are involved in a large-scale operation, including response management staff, responders, partner agencies, expert consultants, stakeholders, affected populations, political leaders, and the public. Each segment has unique information requirements that response organizations have the responsibility to fulfill. Being able to effectively collect, process, manage, and disseminate information is considered by emergency managers to be of paramount importance to overall mission success.[74, 80, 81] The wide array of partners, stakeholders, and customers requires that emergency management organizations have the ability to connect, integrate, and disseminate information across different systems. Ideally, federal, regional, state, and local partners, as well as various types of healthcare organizations, can access unified information systems, but privacy, security, proprietary material, and government concerns limit our ability to open some networks to the full list of participants in medical disaster response. We must therefore strive to share platforms whenever possible. However, established linkages through operation centers and other communication is also an effective means to ensure the flow of operational information with all partners.

An information management and communication plan is an important aspect of information management and communication. The plan should address various considerations, including management of medical information, schedules for recurring communications, and parameters and issues associated with the release of information to the public and the press. Discussions and coordination should occur prior to an incident, to determine how health and medical information is to be managed and distributed during response.[80] The second consideration is the establishment of an operational tempo of coordination and information-exchange activities. Every response should have a set of coordination activities – calls, meetings, and reports – for the exchange of information and the status of operations. Also worth noting is that the health and medical emergency activities are usually part of a larger multidiscipline response. As health and medical disaster response professionals, we must keep the higher-level response operation personnel and leadership informed of our operations and our issues.[82] A third and likely more important issue is the release of information to the public. An effective information management plan will ensure the coordination of messaging. A long history exists of problems in response operations when different and often conflicting messages get sent by different elements of local, state, or federal government, or by other officials.[82]

The modern era allows for many technological tools to support information management. One area that is growing in importance is that of social media. Although many response organizations are reluctant to embrace social media due to its potential unreliability, others are learning how to make use of this valuable resource. Trust is a key issue. A few means to improve trust and increase the likelihood of validity of social media information are (a) to use only aggregate data that shows trends, (b) to only accept information that can be confirmed from several independent sources, or (c) to validate it against known reliable sources.[83] The possibility to receive real-time on-scene information is too important to ignore. Case studies and after-action reports have demonstrated the utility of social media in disaster response.[69, 84] Another use of social media is to disseminate information. Social media has been demonstrated to be an effective tool for dissemination of information in disasters.[74, 81] Emergency managers must understand that that mobile communications and social media are the primary means of communication for a growing segment of the population, and that segment will use it during disasters or public health threats.[85]

The nature of disaster response has changed in recent years to be more intensive, more comprehensive, and more reliant on information management. While the face of each disaster is unique, each will certainly require more knowledge, skills, and abilities than comparable incidents just a generation ago. We continue to succeed in our most crucial of occupations only through continuous after-action review and improvement, the use of an ever-expanding set of expert resources, and a mastery of information management and communication. Providing health and medical support to people when they need it most is a near-sacred charge. As response professionals, we need to continue to enhance capabilities and proficiency to meet the changing face of disaster response.

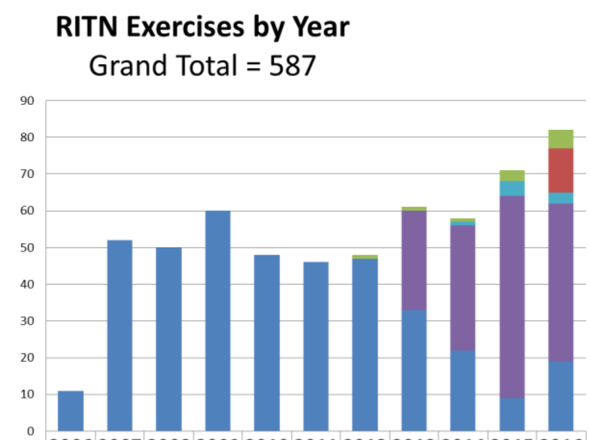
Surge and healthcare coalition

The Hospital Preparedness Program (HPP) is one of two federally funded cooperative agreements to states, selected cities, and the territories and freely associated states intended to specifically support planning for disasters and large-scale emergencies. Through cooperative agreement funds, over 400 healthcare coalitions across the nation have been funded to develop an approach to large-scale disaster planning, response, and recovery. Keeping with the maxim that "all disasters are local," this activity emphasizes the combination of local and regional considerations, with the importance of ensuring a coordinated, interdisciplinary systems approach to crisis incident management. A key element in planning has been cooperative agreement funding to support the development of "healthcare coalitions," which are groups of individual healthcare and response organizations in a defined geographic location.[86] Core healthcare coalition membership comprises hospitals, emergency medical services (EMS), public health agencies, and emergency management organizations. With at least two hospitals as members in any given coalition, the intent is to ensure the ability to distribute patients based on availability and capability, should the demand for healthcare services in any location exceed available supply. Healthcare coalitions play a critical role in developing health care delivery system preparedness and response capabilities for "all-hazards" disaster incidents and are particularly beneficial in helping to augment information-sharing; resource-sharing, -allocation, and -management; and education and training for first receivers.

Seeking to improve upon the success of the healthcare coalitions and demonstrate a better approach to disaster medical care, ASPR recently funded a two pilot programs to develop a Regional Disaster Health Response System (RDHRS). The RDHRS draws on the existing U.S. healthcare infrastructure, pulling together private sector and federal resources and builds on local healthcare coalitions and trauma centers, creating a tiered system of disaster care. It will integrate local medical response capabilities with emergency medical services, burn centers, pediatric hospitals, labs, and outpatient services, to meet the overwhelming health care needs created by disasters (https://www.phe.gov/Preparedness/planning/RDHRS/Pages/rdhrs-overview.aspx).

Specialist contribution

Given the magnitude of a nuclear or large-scale radiation incident and the need to have extensive expertise and care available, a "just-in-time" approach would be unacceptable. A pioneering example of public-academic-private collaboration is RITN. Since it was founded in 2006, exercises are a part of the annual work done at each RITN center (Figure 2). The exercise program grew from an annual tabletop exercise organized by RITN for each hospital, blood donor center, and cord blood bank to conduct on their own, to now include full-scale, functional regional tabletop exercises. For the initial tabletop exercises each year all participating centers provided responses to set questions that were collected via a web-based survey tool. Beginning in 2012, RITN offered funds to RITN hospitals to conduct radiological/nuclear scenario full-scale exercises, and in 2014 RITN coordinated its first regional tabletop exercise. The regional tabletop exercises bring together the community (e.g., adjacent hospitals, emergency management, public health, federal agencies, and non-governmental organizations; collectively these are called voluntary organizations active in disasters [VOADs]) to discuss how they would receive a surge of casualties from a radiological/nuclear incident requiring care in their community. Many metropolitan cities had discussed responding to a radiological or nuclear incident if it occurred in their community, but not what would happen if the incident was 2,000 miles away and then the medical surge was brought to them. All exercise materials and after-action reports are posted on the RITN website (https://ritn.net/exercises/) for use by any organization that would benefit from the RITN's activities.



	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Fullscale							1	1	1	3	5
Functional											12
Regional Tabletop									1	4	3
Web-based Tabletop								27	34	55	43
Tabletop	11	52	50	60	48	46	47	33	22	9	19

Figure 2: RITN exercises held per year: 2006 – 2016

The expertise of the hematology/oncology communities has been organized to provide medical care through the RITN to casualties, without trauma, exposed to marrow-toxic doses of radiation. While estimates [42] suggest only about 1% of victims could eventually require a stem cell transplant, tens of thousands more would be eligible for monitoring and specialized therapeutic/supportive care. Stratification of survivors for treatment is based on estimates of radiation dose. Detailed computer models, such as from the National Atmospheric Release Advisory Center (NARAC; https://narac.llnl.gov/), were developed for estimation of mass exposure from type, size, and locations of nuclear detonations, and meteorological and topographic factors affecting trajectory of the plume. Rapid biodosimetry technology for individual dose-estimation, however, has been limited. Lymphocyte count sampling in the first 24–48 hours for pattern of decline may not be achievable during 'sheltering-in-place' and mobilization of point-of-care resources. Furthermore, administration of granulocyte colony-stimulating factor (G-CSF) was shown in early trials to alter blood lymphocyte counts. Dicentric quantification has limited availability and is resource- and time-consuming. Identification of biomarkers and focus on rapid and high-throughput genomic and proteomic technology has been in development for almost 10 years and has yet to come to fruition. Questions arise about appropriate use of stockpiled medications and growth factors, which will likely be in limited supply, for clinical complications, including who should dispense MCMs, when, and the ethics of who should receive them. Recent data on granulocyte-macrophage colony-stimulating factor (GM-CSF) appears promising (unpublished), but whether this will significantly impact the stockpile of growth factors and a recommendation for administration of growth factors on day one is unclear.

<u>Rad responders: On-scene radiation incident responders and the Radiation Emergency Assistance Center and Training Site (REAC/TS)</u>

On-scene response is designed to be flexible and scalable in relationship to the size of the radiological/nuclear incident. All radiological/nuclear incidents are local, meaning that local responders will be the first to arrive on the scene.[87] They will include emergency medical technicians, HAZMAT teams, fire/police, healthcare professionals who are trained to staff clinical reception centers, and in some states, volunteers who are members of local medical reserve corps units. Depending on the size of the incident, the state governor may activate the National Guard which may become federalized to provide a seamless response directed by the armed forces. Many states, including those with a nuclear power plant, participate in the Emergency Management Assistance Compact (EMAC) to provide interstate mutual aid that may include on-scene assistance.

Help from federal assets will take time. The Advisory Team for Environment, Food and Health (A-Team), a radiological emergency response group, will develop recommendations for the

Incident Command/Unified Command and local and/or state authorities, as appropriate. The National Response Framework (NRF)[88] provides a unified approach to mobilizing assets from the U.S. in the case of a large-scale catastrophe.[89] As the lead agency for the NRF's Emergency Support Function 8 (ESF 8)[90] addressing public health and medical services, DHHS will provide representatives on-scene to perform medical needs assessments of affected areas, provide advice on triage and medical management of casualties, establish reporting activities for patient movement, initiate the movement process, and coordinate all aspects of the medical and public health response in coordination with the RITN and the National Disaster Medical System (NDMS). This includes making MCMs available through deployment from the SNS.

As supporting federal agencies for ESF 8, the DOE, DHS, and DoD may become activated. From the DOE, members of several U.S. government agencies will arrive, including the Federal Radiological Monitoring and Assessment Center (FRMAC),[91] an interagency asset, to coordinate ground and aviation-based environmental radiological monitoring; the Radiological Assistance Program teams from one or more of eight regions nationally (part of the National Nuclear Security Administration); and one or two emergency response teams (each consisting of a physician, a nurse-paramedic and a health physicist) from the Radiation Emergency Assistance Center and Training Site (REAC/TS)[92] to provide medical advice to clinical leadership and support response workers from the FRMAC. From the DHS, SMEs from one or more of FEMA's ten sites in the U.S. and the Mobile Emergency Response Support program will provide on-scene assistance.

From the DoD, Weapons of Mass Destruction Civil Support Teams may be activated at the direction of the governor. They will have technical and analytical reach-back and may be incorporated into joint DoD units consisting of Army National Guard and Air National Guard personnel. Depending on the nature of the incident, the DoD may elect to activate agencies within the Department, as well as establish a national defense area and/or a Joint Field Office on-site. In addition, as part of the nation's NDMS for patient care and movement, approximately 10 physicians and 20 health physicists from the Veterans Administration Medical Emergency Radiological Response Team (MERRT),[93] Disaster Medical Assistance Teams,[94] and volunteers from the Medical Reserve Corps (MRC) would be available on-scene, as needed. Under the MRC, specialized Radiation Response Volunteer Corps (RRVC) Teams have been established in 24 states. Other specialized teams will be also available, if needed, including the Disaster Mortuary Operational Response Teams (DMORT), the National Veterinary Response Team (NVRT), and the Trauma Critical Care Teams (TCCT). Additionally, The U.S. Public Health Service (USPHS) has a number of deployable teams to support and conduct field operations. These include Rapid Deployment Forces (RDF), Applied Public Health Teams (APHT), Mental Health Teams (MHT), Services Access Teams (SAT), and National and Regional Incident Support Teams (NIST and RIST, respectively).

Real-world perspective and experience

Practical assumptions that should govern the development of CONOPS for response to a CBRNE attack should focus on the importance of information sharing, establishment of a common operating picture, and the development of good situational awareness amongst the many local stakeholder response entities involved. In addition, the timely movement of life-saving medical resources, both durable medical supplies as well as specific MCMs, needs to be prioritized. Local stakeholders, in both the public and private sectors, will likely have limited resources and expertise to be able to establish a purposeful response without such input. Although, as is noted elsewhere in this article, response is fundamentally local, increasingly clear is that "day after" actions for a CBRNE incident of substantial magnitude and gravity require a strong federal response in which federal personnel take charge early and manage the response with authoritative and definite actions.

An urban area nuclear detonation can serve here as an example case-in-point. The sheer number of fatalities, in addition to casualties requiring emergent care will place a significant strain on medical surge capacity and capability. Add to this the anticipated breakdown in communication systems, overwhelming stress on transportation systems attempting to accommodate those trying to evacuate, and the significant impact such an incident will have on commerce and economic stability. General fear, panic, hysteria, and civil disorder will likely sweep the country, both in revulsion to the attack that has occurred, as well as in anticipation that another attack could happen anywhere, anytime. Three leading voices in the defense establishment correctly pointed out a decade ago, in their article surmising the effects of a nuclear attack on a U.S. urban population, the importance of federal government leadership:

> The federal government should stop pretending that state and local officials will be able to control the situation on the Day After. The pretense persists in Washington…that its role is to 'support' governors and mayors, who will retain authority and responsibility in the affected area. While this is a reasonable application of our federal system to small and medium-sized emergencies, it is not appropriate for large disasters like a nuclear detonation.[95]

Of course, the roles of local and state responders will be critically important, as all disasters are ultimately defined by the local impacts that result. The principles of limited government and federalism dictate that local communities have the single most important role in shaping local preparedness plans, policies, and procedures. But in an incident of this type, and in the context that we are still learning from the response to Hurricane Katrina that occurred well over a decade ago, relevant federal assets must be pressed into service, and quickly. These interactions during an incident should follow tried and true recognized protocols that place the jurisdictional emergency manager at the center of such discussions. The state emergency management agency will also play an essential coordinating role, particularly as it relates to the state response, and its facility to connect federal resources, both materiel as well as human, to the local community.

Just-in-time knowledge

The various tools and guides were described in the main paper, including REMM (https://www.remm.nlm.gov/) and CHEMM (https://chemm.nlm.nih.gov/) web resources, and *A Decision Makers Guide: Medical Planning and Response for a Nuclear Detonation* (https://www.remm.nlm.gov/decisionmakersguide.htm).[96] Critical to the utility of these resources is ongoing updates of the content and the adaptability of their platforms for use on computers, tablet computers, and smart-phones. This allows them to be accessible despite communication interruptions.

Element 5: Recovery and Resilience

The following activities are key components of the capability for recovery and resilience:

- Community engagement
- Early use of a recovery plan
- Assessment of infrastructure priorities
- Psychological support for populations and responders

Recovery and resilience

All disasters are local; therefore, all response actions are directed, informed, or otherwise influenced by the local context and community constructs. Long after response actions have concluded, the lasting impacts of a CBRNE incident are felt at the individual and household level. The direct responsibility of recovery is often led and directed (in the macro sense) by government entities or leadership, whereas the resilience of the community-based structures are more reliant upon a diffuse network of independent bodies or actors, often without a formal government affiliation.[97] While government bears the burden for establishing the environment contributing to a "successful" recovery, the networks of other connections are essential to ensure the development of adaptive capacity to recover in supporting a resilient population.[98]

The interplay between disaster recovery operations and enhancing community resilience can be challenging to negotiate due to pre-incident conditions (i.e., social and economic vitality), post-incident realities (i.e., future threat environment and community risk perception) and governance (i.e., political, private leadership engagement and support over time). Implementation of an effective recovery operation process that enhances community resilience after a CBRNE incident requires intimate policy awareness and operational coordination between "non-traditional" disaster managers, government leadership, non-government practitioners, and the direct engagement of community members themselves.

The ability of an impacted community to "bounce back" has been shown to be a direct reflection of the degree of community civil engagement,[99] the existence of strong pre-incident bonds or nascent threads of connectivity between and across community organizational constructs,[100] and the ability to rapidly identify and apply the appropriate policy and fiscal programs and strategies to address current challenges with a shared vision toward mitigating future hazards and vulnerabilities.[101]

Often lost in disaster recovery discussions is the impact of the incident on health and social service networks beyond bricks and mortar, understanding of the individual human, population health implications of subsequent planning decisions, and recognizing the meaningful contributions a health-centered approach could have on the recovery process.[102]

As highlighted by Chandra et.al.[98] developing community resilience can be connected to concepts of access (to high-quality health care, behavioral health, and social services); education (in the form of public information on preparedness, risks, and resources before, during, and after a disaster); engagement (participatory decision-making that extends from planning to response and throughout recovery); self-sufficiency (to activate individual agency and self-determination); partnership (facilitating vertical and horizontal linkages); and efficiency (leveraging existing community resources for maximum use and effectiveness).

Successful recovery operations that have utilized health assessment of engagement processes to build resilient communities include those of (a) Cedar Rapids, Iowa, following their 2008 floods, as they leveraged the Model Approach to Partnerships in Parenting (MAPP) and the Community and Regional Resilience Institute (CARRI) process as part of their community redevelopment planning; and (b) Little Egg Harbor and Hoboken, New Jersey, which utilized Health Impact Assessments in partnership with Rutgers University to inform their community redevelopment decision-making process.

Disaster recovery is a non-linear process for conventional disasters, as well as for a CBRNE incident. The ability to predict and adapt to the evolving stress environment in the subsequent months and years rests on the ability of various actors across domains to negotiate collectively through myriad challenges. Success can be fostered by adopting elements from health care (e.g., patient-centered approaches) and public health (e.g., community engagement and health assessment strategies), and by understanding the impact on the individual.

Public health

Every large-scale disaster, irrespective of etiology, can be fairly characterized as a public health crisis. The central reality of any calamitous incident is that great numbers of lives are in jeopardy. In our definition of a megadisaster, in which lives are at stake and rescue resources are required from outside the community or region, the key criteria for assessing the severity of the crisis are the presence or absence of the following abilities, in order of priority:

1. Rescue survivors
2. Secure critical medical care for rescued survivors
3. Stabilize and sustain needs of vulnerable populations, including individuals with chronic illness
4. Protect or rapidly restore critical infrastructure
5. Sustain social order

Whether the incident is a natural disaster, the emergence of a deadly epidemic, a high-level industrial accident, a catastrophic infrastructure failure, or a major terror attack, the primary initial concerns all relate to the survival and well-being of people who have been or may be exposed to the impact. This should be understood from the perspectives of prevention, mitigation, and response; a classic public health, population-based approach.

Prevention spans an enormous spectrum ranging from primary prevention of the incident in the first place (such as by enhancing resiliency of infrastructure or development of a universal flu vaccine) to taking appropriate shelter from a large-scale radiation incident, promoting measures to reduce spread of a lethal flu, or preparing populations to shelter-in-place or evacuate as part of effective disaster planning. The point is to do whatever is necessary to save lives and prevent injury.

Nevertheless, a prepared healthcare delivery system is an essential component of CBRNE response capability. In terms of preparedness for response to CBRNE incidents, the concept of public health should include the healthcare delivery system, its broad capabilities, its resiliency, and its ability to function in response to a wide range of CBRNE-related disasters. However, "good" health care in the absence of a highly functioning public health system (federal, state, and local components) is insufficient in planning for CBRNE. The converse is also true. No amount of "readiness" among local and state public health agencies or the CDC with respect to traditional public health functions (e.g., surveillance, communications, strategic stockpiles of MCMs) will replace or minimize the need for a highly capable direct health services capacity.

Public health, therefore, can usefully be considered to include the direct medical systems when it comes to planning or preparing for or responding to major CBRNE incidents.

Currently, the status of public health readiness is fragile and insufficient. Funding prospects for essential research, hospital and provider training, and readiness are at dangerously low levels. Horizontal coordination among governmental agencies at all levels, local, state, and federal, remains severely problematic, as is vertical coordination among government agencies.

Psychosocial factors

Psychosocial factors are an integral part of preparedness for, response to, and recovery from CBRNE incidents. Because these factors influence how people respond, they impact not only individual and community recovery, but also how the incident itself unfolds. Research and recommendations on CBRNE have tended to be embedded in articles about broader psychosocial issues in natural and manmade disasters, focusing primarily on (1) provision of mental health services, (2) incident characteristics that impact psychological response, and (3) risk communications.[103]

Gouweloos and her colleagues (2014),[104] examined 39 studies published between 2000 and 2013 addressing psychosocial care in CBRN incidents. Their review found no studies which met the criteria for effectiveness research, but they found strong consistency of recommendations. These recommendations, in general, are like those made in response to other kinds of disasters, with an emphasis on training and education of responders, support to victims, and psychosocial counseling for impacted individuals and communities. CBRN incidents were unique in the emphasis on risk communication and the need for specific preparation for addressing uncertainty about health effects, contamination, worker reluctance to respond, and the possibility of panic.

The characteristics of a CBRNE incident greatly influence the best strategies for preparing. In certain incidents that are likely to produce high anxiety, such as a radiological attack, “psychological casualties” may result who are unexposed but still display symptoms and seek help. In other scenarios, such as a biological incident, healthcare workers may have contagion concerns that influence their ability to respond. Although all-hazard planning remains an essential starting point, the psychosocial concerns of specific types of scenarios need to be integrated into planning, so that scenario-specific concerns can be anticipated and planned.

The issues above underscore why risk communication is so critical. Challenges in effective risk communication influence the evolution of the incident, especially in a media environment that provides extensive information about risks but little guidance on how to understand the risks. Because of advances in research and theory, the area of risk communication has developed substantially in recent years.[105] Recommendations in this area focus on engaging the public, promoting adaptive responses, and providing information that promotes physical and psychological safety.

Program evaluation

Evaluation is a process by which we critically examine a program. Key activities in evaluation include systematic and comprehensive collection and analysis of data related to a program's activities, reporting the results, and determining if the program's outcomes are aligned with the organization's strategic goals. The process of evaluation is an important organizational component that can help to improve programs and hold public managers accountable to taxpayers. Evaluation can help strengthen the program along three phases of its life cycle: (1) the pre-decisional or planning phase, (2) the post-decision or formative phase, and (3) at the completion or summative phase. ASPR conducts evaluation at all these phases of a program's life cycle.

ASPR leads the PHEMCE, the federal MCM enterprise centered on four DHHS agencies (ASPR/BARDA, NIAID, CDC, and FDA), as well as containing elements of other federal departments. These DHHS agencies annually spend over $4 billion for research, development, stockpiling, planning for, and effectively using MCMs that address CBRN threats. The ASPR policy and program evaluation experts develop economic studies and decision analytic tools to assist in the allocation of scarce national health security dollars targeted to the federal MCM enterprise.

ASPR developed initial decision support tools in 2012 to prioritize and recommend MCM stockpiling investments for the SNS Annual Review process. These tools include: (1) a comprehensive data system with key MCM operational and life-cycle management characteristics and multi-year cost projections, to assist SMEs and senior leaders in prioritizing MCM stockpiling decisions; and (2) a risk-based relative priority index for prioritizing the acquisition of MCMs and optimizing stockpiled MCM investments in the portfolio within each threat area and among threat areas.

In 2014, the PHEMCE approved a groundbreaking mechanical ventilator operational capacity assessment.[44] The ventilator assessment projects the nation's healthcare system surge capacity for ventilator use, identifies capability gaps, and identifies solutions for closing those gaps in the case of a national pandemic influenza outbreak. Identifying surge capacity constraints helps to ensure the federal government does not acquire more MCMs than can be effectively used in a public health emergency, enabling savings to be allocated to other high-priority MCMs. Due to the ventilator assessment, the concept of operational capacity has been adopted formally as a key determinant in the strategic level preparedness assessments and for the requirements process in support of MCM acquisitions.

In 2015 the DHHS Office of the Secretary's Ventures Program funded a study[106] to identify potential economic spillover benefits in the day-to-day healthcare system for an investment by BARDA in a burn debridement product for use in an improvised nuclear device incident. Building on this study, activities are underway to assess the economic impact of additional BARDA burn portfolio investments.

Element 6: Lessons Learned

These are key components of lessons learned:

- Realistic and honest assessment of exercises and incidents at all levels
- Publication of results

The conceptual approaches and models that inform planning, and the resulting planning itself, face the reality for which they are designed when an incident occurs. Exercises designed to simulate key elements of real incidents provide opportunities to test the suitability of the approaches, models, and planning prior to realization of the actual risk of an incident, allowing important enhancement of readiness. However, exercises have artificiality, and often only a limited set of components can be included. The best learning comes from experience with honest and open discussions held following an incident (unscheduled) or event (planned; e.g., inauguration). These discussions include one's immediate impressions as to gaps and needs shared in the "hot wash" immediately following the incident or event, and the longer-term enhancements and activities needed from training, exercises, and lessons-learned (TELL).

While experience and impressions are good teachers, rigor and a strong evidence-base are important both to describe the information used and for one's ability to access what may be obscure information. Experts in searching and evaluating identified information and the presentation and organization are critical.

TELL

An effective mechanism for ensuring jurisdictions are prepared for a potential disaster is what the emergency management enterprise refers to as the preparedness cycle –a continuous cycle of planning, organizing, training, equipping, exercising, evaluating, and taking corrective action feeding back into planning, with the intent of improving readiness and preparedness.

Success in the evaluative and corrective elements of the cycle ensures department-wide preparedness and improvement as we capture lessons-learned and apply them to sustaining and strengthening the health and emergency response systems, leading to a stronger community resiliency.

The evaluation is best conducted using a non-attributional "hot wash." The hot wash is the immediate open and honest discussions and assessment of performance following an exercise, training session, or major incident. It is not as useful in the form of a critique in the form of fault-finding with a negative connotation. The culmination of the hot wash and the evaluation is an "after-action review" (AAR) – a formal, structured review document that describes what happened, why it happened, and how it can be done better by the participants and those responsible for the response. Within the lessons-learned process, the implementation of corrective actions is the goal for realizing the improvement that can result from exercises and real-world incidents informing all preparedness-cycle components. Corrective actions are the concrete, actionable steps outlined in improvement plans designed to resolve preparedness gaps and shortcomings. The corrective action program (CAP) enables users to prioritize, track, and analyze improvement plans developed from exercises and real-world incidents. The primary goal of the system is to help officials resolve preparedness gaps or deficiencies in a systematic manner, ultimately strengthening overall preparedness. CMOSSE participation helps share lessons learned and CAPs across agencies and also among federal, regional, state, local, and also global SMEs.

Medical decision model for recommending policy, based on Japan experience

The value of preparedness, planning, and pre-established experience among SMEs was demonstrated at the U.S. embassy response to the March 2011 nuclear power plant disaster in Japan. Representatives from a multi-agency team provided advice to the U.S. ambassador in Tokyo and to their respective agencies in the U.S., and also provided town-hall style meetings at the U.S.-Japan Chamber of Commerce in Tokyo. Among the lessons learned was the importance for decision-makers to be in face-to-face contact with SMEs who are comfortable making decisions based on rapidly evolving information, communicating succinctly and clearly to the public, and changing direction and message as new knowledge emerges. This led to a unique medical decision model.[107] Based on the need for decision-makers to become familiar with a complex body of knowledge, a decision-makers' guide (DMG) has been prepared,[108, 109] and a fully navigable electronic version is available.

Library science

ASPR's Technical Resources, Assistance Center, and Information Exchange (TRACIE; https://asprtracie.hhs.gov/), launched in September 2015, provides evidence-based applications, technology, and proven best practices to provide stakeholders with the information they need to improve their knowledge and effectiveness. TRACIE provides topic collections and technical assistance to local, state, regional, tribal, and federal staff, healthcare associations, and others on a variety of topics such as mass-casualty incidents, CBRNE issues, crisis standards of care, healthcare coalition development, plan examples and templates, hazard vulnerability assessments, and communications. TRACIE disseminates assistance and products through a coordinated system, including the following elements:

- An SME cadre
- SME-validated publications in the resource library
- Topic collections (SME-reviewed annotated bibliographies that include links to plans, templates, educational materials, and other resources; e.g., Radiological and Nuclear and Explosives and Mass Shooting)
- *The Exchange*, an online newsletter that features lessons learned from practitioners in the field

- Live and pre-recorded webinars (e.g., Healthcare Coalition Involvement in Mass Gatherings and Cybersecurity and Healthcare Facilities Roundtable)
- Facilitated, on-line peer-to-peer engagement and support through the password-protected Information Exchange
- Guidance documents, fact sheets, and illustrative examples of promising practices (e.g., CMS Emergency Preparedness Rule Resource at Your Fingertips and HIPAA and Disasters: What Emergency Professionals Need to Know)

Element 7: Continuous Improvement

These are key components of continuous improvement:

- Development, modification, and implementation of new plans from lessons learned at all levels
- Assessment of other countries' plans
- Integration of new science
- No fear of new strategies
- Adequate financial commitment

With all that happens in the components of disaster medicine, active ongoing action and collaboration is essential to be certain that the best available science and knowledge are being applied and gaps are recognized and addressed. The scope of expertise and drive for new knowledge and improvement are pursued by the range of experts and programs from academia, professional societies, community experts, and responders. Examples of ongoing activities are provided.

Nuclear Incident Management Enterprise (NIME)

Complex material is contained in the NIME publication,[110] the integration of which is a demonstration of the need for the establishment of CBRNE science. It is a systematic approach built on the available and emerging science that considers physical infrastructure damage, the spectrum of injuries, a scarce-resources setting, the need for decision-making in the face of a rapidly evolving situation with limited information early on, timely communication, and the need for tools and just-in-time information for responders. Responders will likely be unfamiliar with radiation medicine and uncertain and overwhelmed in the face of the great number of casualties and the presence of radioactivity. The components of NIME, which are a continuous work-in-progress, can be used to support planning for, response to, and recovery from the effects of a nuclear incident.[110]

Knowledge- NIH - Disaster Research Response (DR2) Project, with the Intra-NIH Disaster Interest Group (I-DIG)

The DR2 Program (led by the National Institute of Environmental Health Science [NIEHS] in collaboration with NLM) was initiated in response to a call-to-arms by Drs. Lurie, Collins, and Frieden in 2013 regarding the need for "Research as Part of Public Health Emergency Response."[111] Since initiation in 2014, the NIH DR2 Program has made significant progress and worthy national contributions toward its focus of promoting timely health research on the medical and public health aspects of disasters and public health emergencies. These are among the key objectives for the DR2 Program:

1. Rapid identification of important research gaps, questions, and priorities
2. Improvement of quick access to data-collection tools, institutional review board-reviewed protocols, guidance for researchers, and qualified members of the public

3. Health and safety training of clinicians and researchers to participate in disaster-related field studies
4. Integration of research response activities into the National Response and Recovery Frameworks and activities
5. Establishment of transdisciplinary disaster research networks of clinicians, public health, academia, non-governmental organizations, and communities to help with the collection of time-critical information to support response and recovery activities

Major accomplishments of the DR2 Program include (1) a publicly accessible website containing about 350 data collection tools for surveys, questionnaires, forms, reference materials, and other products useful for medical and public health research following disasters (https://dr2.nlm.nih.gov/); (2) new training information for research responders (https://www.niehs.nih.gov/about/events/pastmtg/hazmat/assets/2016/wtp_spring_dr2p_boston_participant_manual_finalv2_508.pdf), and (3) novel research response exercises in Los Angeles, Houston, and Boston, including over 300 participants from academia, state, and local agencies, industry, responders, and the broader community (https://tools.niehs.nih.gov/wetp/index.cfm?id=2574#DR2).

Furthermore as part of the DR2 program activities, the I-DIG was developed to facilitate relationships and collaborations across NIH institutes to promote transdisciplinary exchange of information to support disaster research processes, implementation, and studies. The I-DIG meets monthly to discuss disaster-related research issues and consists of 65 NIH staff and scientists from 15 institutes.

Accessing the experts

Scientists and engineers at universities and national laboratories serve as SMEs for CBRNE science and engineering. Many of these experts reside at the DOE national laboratories. They devote their careers to research and development to support federal department and agency agendas and national security strategies. They fill in the gaps of incomplete knowledge and provide new understanding with rich research, applications science, and implementation program comprehension.

Access to SMEs at national labs associated with the federal enterprise as FFRDCs is straightforward. The SMEs can be contracted to support research and development directly via any department or agency, but DOE, DHS, DoD, and DHHS are the primary sponsors of research contracted to the labs. SMEs often serve the nation as Intergovernmental Personnel Act Mobility Program representatives (https://www.usgs.gov/about/organization/science-support/human-capital/intergovernmental-personnel-act-ipa-mobility) and act as federal employees in non-federal offices. In this case, the expert acts as a federal employee for a defined number of years and is prohibited by conflict-of-interest considerations to show favor to the home lab. SMEs can lend their expertise to support any federal department or agency, including the Office of Science and Technology Policy in the Executive Office of the President.

Another avenue to gain access to SMEs is via professional societies or congressionally chartered councils. The NCRP provides an exceptional example. The NCRP stands ready to serve the nation on national security topics to support federal decision-makers. The NCRP maintains seven program area committees (PACs; http://ncrponline.org/program-areas/) that meet frequently to ensure that experts stay versed in the needs of the nation and are ready to serve as advisors. Especially focused on CBRNE topics is PAC-3, Nuclear and Radiological Security and Safety.

ASPR is organizing SMEs from within and outside government who will be available should their expertise be needed. The group is the ASPR CBRNE Expert Science (ACES) group.

A number of professional societies have interests in disaster medicine and emergency medicine. These include: the Society for Disaster Medicine and Public Health, the Society for Academic Emergency Medicine (SAEM), and the American College of Emergency Physicians (ACEP).

Programs and divisions in disaster medicine exist, often within emergency medicine departments and/or schools of public health globally; examples include Johns Hopkins University[112] and Harvard University's T.H. Chan School of Public Health.[113]

From evolving need, going back to the lab

As illustrated in Figure 1 in the main paper, CBRNE science improves through experience that translates into improved tools, practices, procedures, and medical interventions that result from ongoing laboratory and clinical research. MCMs serve as an example. The introduction of vaccines, diagnostics, and other MCMs can have enormous impact on the consequences of a CBRNE incident and require major changes to the CONOPS. The national CONOPS approach is to have a template upon which changes can be readily made, the information disseminated, and planning and response operations modified to take advantage of the new capabilities. CMOSSE will be integral to bringing science into preparedness, operations, and resilience.

Similar to practices outlined for the other areas of preparedness, an iterative process is necessary to ensure that MCMs are effective, safe, and relevant to evolving CONOPS. Over the past two decades we have seen several components of MCM development evolve, including development of animal models to assess efficacy, the development and guidance of the Animal Rule from the FDA, and advances in our understanding of the natural history of radiation injury. Changes in all of these areas have required MCM developers to remain flexible and open to reevaluating MCMs in new evolving contexts.

Gradually becoming clear is that after MCMs for treating pancytopenia, developing the next class of MCMs will require a deeper understanding of radiation injury. NIAID, BARDA, and other PHEMCE partners have supported many MCMs in early- to late-stage development and the FDA often has noted in its comments about these MCMs a lack of understanding of the mechanism of action or of the relationship between the mechanism of action and mitigation of radiation injury. New efforts in MCM development require a deeper understanding of radiation injury, including a more cellular physiological basis of understanding. This is a poignant example of late-stage development needing to pause and consider "going back to the lab." Coordinating MCM activities and dialog across the PHEMCE is enabling new foci and targeted natural history efforts to address identification of new etiologies and MCM targets, and establishment of a new product-development pipeline. The inter- and intra-agency coordination and partnerships with academia and industry have been critical in empowering these activities. The field of radiation injury is likely heading for a paradigm shift in understanding, from pancytopenia being the primary therapeutic target for radiation injury, toward more cellular physiological processes based in systemic response of the entire body. CBRNE science will be an essential component in driving this evolution of MCM development.

Developing one or more adequate animal models for assessment of an MCM being developed under FDA's Animal Rule is essential. Early challenges have included trying to envision what elements of supportive care might be available during a mass-casualty incident and what the operational windows are for administration of MCMs for them to be effective, with subsequent incorporation into animal models to test MCMs for efficacy. As our understanding of logistics has evolved through CONOPS exercises and discussions across preparedness disciplines, the animal models have been tweaked and modified to more closely represent the conditions we would anticipate in a mass-casualty incident. Preparedness exercises have underscored the importance of a flexible operational window for MCM administration and highlighted some data gaps for existing MCMs that should be addressed. Early animal model activities have stressed the importance of supportive care elements, whereas exercises have identified preparedness gaps for these elements that should become priorities for MCM and logistics development. This process will continue and CONOPS and subsequent MCM testing will need to continue to evolve together to ensure robust preparedness.

Conclusions and Looking Ahead

The primary conclusions and next steps for CBRNE science are outlined in the main paper. The details of the seven elements of CBRNE science in this appendix are for potential use by a working group to discuss formalization of the CMOSSE. Details matter, even without an official "board certification," as they provide guidance for what is needed in the overarching skill set of a CMOSSE. The changes in disaster medicine and emergency response since September 11, 2001, have been remarkable. Going to broad-based participation among public and private sectors has made the U.S. and the world better prepared; nonetheless, threats will remain and evolve. The transformational approach in CBRNE science and CMOSSE is making the science of the components of health and medical disaster response a foundation for real-time functionality, and a key element of effective response leadership, rather than an ancillary add-on to emergency response. All components in disaster medicine and emergency response are part of a living complex system. CBRNE scientists have broad content knowledge, a systems approach, and ability to be on-the-spot. CBRNE science is a global activity requiring partnerships around the world. It embodies the need for continuous attention, collaboration, and shared ideas and progress.

In closing, we provide a comment from George Korch, whose experience, vision, and wisdom provide an outstanding perspective regarding this concept:

> Planning response to the unthinkable must be rendered into the realm of thinkable. The overused cliché that no plan survives first contact with the issue (enemy) belies the central truth that lack of planning is not a viable alternate strategy. How things have worked, and how things will work in the future have the commonalities that one has to mentally and metaphysically put oneself into that unthinkable situation and test the notions of what that reality would look like in the context of the combined activities of others doing the same. In addition, this has to be done repeatedly to challenge what the "established" thinking looks like against changing threat scenarios, people, and technology. Effective planning must be done with a total mental commitment to being in that horrible moment when hypothetical becomes actual. The question then becomes not "*How has this worked?*" but "*How has this kept working?*" What have been the underlying strengths of the response system that has kept going in the face of an enormous disaster and what interventions or changes can be made to make the response and resilience even better?

Next steps

At the time of writing this manuscript, the projected next steps are to consider how best to bring together interested organizations to consider possible implementation and formalization of

CBRNE science and the CMOSSE. Among the next steps are presentations at professional society meetings, including the Society of Disaster Medicine and Public Health at its annual meeting. Communication to the ASPR subject matter experts including the co-authors (CN Coleman, JF Koerner, C Hrdina, and KD Cliffer) is welcomed.

Abbreviations and Acronyms

AAR	after-action review
ACEP	American College of Emergency Physicians
ACES	ASPR CBRNE Expert Science
AFRRI	Armed Forces Radiobiology Research Institute (Department of Defense)
ASPR	Assistant Secretary for Preparedness and Response (under DHHS)
ASTHO	Association of State and Territorial Health Officials
A-Team	Advisory Team for Environment, Food and Health
BARDA	Biomedical Advanced Research and Development Authority (in the Office of the ASPR)
CAP	corrective action program
CBRN	chemical, biological, radiological, and nuclear
CBRNE	chemical, biological, radiological, nuclear, and explosive
CDC	Centers for Disease Control and Prevention (an agency of DHHS)
CHEMM	Chemical Emergency Medical Management
CMCR	Centers for Medical Countermeasures against Radiation
CMOSSE	CBRNE medical operations science support expert
CONOPS	concepts of operations
CRCPD	Conference of Radiation Control Program Directors
CUI	controlled unclassified information

DHS	Department of Homeland Security
DHHS	Department of Health and Human Services
DMG	decision-makers guide
DMPHP	Disaster Medicine and Public Health Preparedness
DoD	U.S. Department of Defense
DOE	U.S. Department of Energy
DR2	Disaster Research Response Program (of NIH)
DTRA	Defense Threat Reduction Agency
EIDs	emerging infectious diseases
EMS	Emergency Medical Services
EPA	Environmental Protection Agency
ESF 8	Emergency Support Function #8, for public health and medical services, for which DHHS is the lead agency
EXEMM	Explosive Emergency Medical Management web site - under development as a resource similar to CHEMM and REMM, for explosive incidents
FDA	Food and Drug Administration (an agency of DHHS)
FEMA	Federal Emergency Management Agency (an agency of DHS)
FFRDCs	federally funded research and development centers (including of DoD and DOE)
FOUO	for official use only

FRMAC	Federal Radiological Monitoring and Assessment Center
GHSA	Global Health Security Agenda
HAZMAT	hazardous materials
I-DIG	Intra-NIH Disaster Interest Group
IMAAC	Interagency Modeling and Atmospheric Assessment Center
IOM	Institute of Medicine, now the National Academy of Medicine
MCM	medical countermeasure
NAACHO	National Association of County and City Health Officials
NAPAPI	North American Plan for Animal and Pandemic Influenza
NCI	National Cancer Institute
NCRP	National Council on Radiation Protection and Measurements
NDMS	National Disaster Medical System
NIAID	National Institute of Allergy and Infectious Diseases (of NIH)
NIEHS	National Institute of Environmental Health Science (of NIH)
NIH	National Institutes of Health (an agency of DHHS)
NIME	Nuclear Incident Management Enterprise
NIMS	National Incident Management System
NLM	National Library of Medicine
NOAA	National Oceanic and Atmospheric Administration
NRF	National Response Framework

OSTP/NDRD	Office of Science and Technology Policy/Nuclear Defense Research and Development
PAC	program area committee (of NCRP)
PAGs	Protective Action Guidelines (EPA)
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise
PHEP	Public Health Emergency Preparedness, a cooperative agreement program managed by CDC's Division of State and Local Readiness
RABRAT	Radiation Bioterrorism Research and Training (NCI and multi-agency)
RAPIDD	Rapid Acquisition of Pre- and Post-Incident Disaster Data
RDB	Research and Development Blueprint (of WHO)
REAC/TS	Radiation Emergency Assistance Center and Training Site
REMM	Radiation Emergency Medical Management web site: https://www.remm.nlm.gov/
RITN	Radiation Injury Treatment Network
RNCP	Radiation and Nuclear Countermeasures Program (of NIAID)
RSS	Radiation Studies Section (of CDC)
RTR	Radiation TRiage, TReatment and TRansport System
SAEM	Society for Academic Emergency Medicine
SME	subject-matter expert
SNS	Strategic National Stockpile

TELL	training, exercises, and lessons-learned
TRACIE	Technical Resources, Assistance Center, and Information Exchange (in the Office of the ASPR)
UMI	User-managed inventory
USGS	United States Geological Survey
VMI	Vendor-managed inventory
VOADS	voluntary organizations active in disasters
WHO	World Health Organization

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