

# National Preparedness and Response Science Board (NPRSB) Medical Countermeasures Preparedness Assessment Report

## Executive Summary

The National Preparedness and Response Science Board (NPRSB), formerly known as the National Biodefense Science Board (NBSB), provides recommendations to the Secretary of the Department of Health and Human Services (HHS) and the Office of the Assistant Secretary for Preparedness and Response (ASPR) and the HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) on strategic preparedness and response to public health threats and medical countermeasure (MCM) needs.

On May 22, 2013, the ASPR tasked the NBSB to make recommendations on how to define realistic preparedness goals that consider the diverse needs posed by various threat scenarios. These goals were intended to inform the development, acquisition, and deployment of critical response-related resources within and by HHS. On January 10, 2014, the NBSB presented a report with recommendations for defining preparedness goals for chemical, biological, radiological, and nuclear (CBRN) threats and for infectious disease-related pandemics. **The centerpiece of the 2014 report was the recommendation that a broad characterization of preparedness and a “whole-systems” approach to goal setting should be adopted, wherein all material, infrastructure, and human components of preparedness are considered as an integrated system.** The basis for this recommendation was the simple principle that a MCM is only useful if it is available, delivered, and appropriately administered within the timeframe that offers efficacy.

In response to the NBSB recommendation, PHEMCE experts designed a MCM preparedness assessment approach and performed a series of four MCM-specific pilot studies. On February 17, 2016, the ASPR issued a task order to the NPRSB requesting a review of the assessment approach and the results of the pilot studies. The task order included three central questions, which are addressed below:

1. *Have we effectively implemented the preparedness assessment process in our pilot studies, particularly with regard to utilization of appropriate assumptions and data sources surrounding the operational capacity to use MCMs?*

**Overall, the NPRSB considers the efforts to create and implement a preparedness assessment process to be highly encouraging.** The process represents the first attempt to link assessments across the entire PHEMCE. The pilot studies relied upon critical insights from multiple agencies. Study inputs also utilized subject matter experts (SMEs) both within and outside the PHEMCE to maximize identification of critical preparedness gaps. The NPRSB commends the Office of the ASPR and other participating agencies for the effort and collaboration required to establish this pilot study process. **However, our overarching observation is that the assessment process does not reflect the urgency that the NPRSB believes is needed to rapidly achieve a comprehensive understanding of our preparedness across threats.** Specifically, each pilot assessment was based on a single MCM and included only a limited set of conditions, rather than a broad range of possible scenarios. The NPRSB strongly favors more extensive assessments. **We consider these assessments to be critical, as informed decisions will enable the appropriate allocation of resources across the PHEMCE. Adequate support for “whole-systems” assessments is essential, even if it requires shifting funding from other aspects of the PHEMCE.** Specifically, the NPRSB recommends:

- 1) Incorporating modeling that more appropriately captures the range of uncertainties
- 2) Performing hands-on exercises to test the validity and shortcomings of model predictions, and
- 3) Vetting the updated assessment approach through a more extensive panel of non-governmental SMEs, including experts in modeling and sensitivity analysis through a convener such as the National Academy of Sciences

2. *Did the preparedness assessment pilots appropriately evaluate current MCM capabilities, and remaining gaps, across the principal components of MCM preparedness?*

The NPRSB feels strongly that **the completion of these pilots was a significant accomplishment, as it required the contributions of SMEs and capabilities across multiple agencies.** As outlined above, the NPRSB strongly encourages the PHEMCE to perform more extensive assessments with additional resources that build upon the momentum from this pilot effort. Specifically, the NPRSB recommends:

- 1) Performing assessments that incorporate the use of all recommended MCMs when applicable for the same event, e.g. both anthrax vaccine and antibiotics for post-exposure prophylaxis
- 2) Modeling permutations to determine how targeted interventions could improve outcomes
- 3) Engaging additional stakeholders, including states and localities, the private sector, and non-profit organizations, to design and perform meaningful exercises that elucidate gaps in operational capacity and inform the design of accurate models, and
- 4) Submitting assessments for review to panels of governmental and non-governmental SMEs

3. *How can we most effectively utilize the results of the preparedness assessments to inform decisions on future investments in MCM preparedness?*

The NPRSB recognizes that careful and informed decisions are essential for maximizing the extent of preparedness given available resources. **The “whole-systems” preparedness assessments should provide the scientific foundation for future investment in MCM preparedness,** which makes it imperative that these assessments are both robust and valid.

Iterative preparedness assessments should guide the balance between dollars spent to stockpile and maintain MCMs, to develop additional MCMs, to provide guidance on the use of MCMs, and to establish and coordinate operational capacity for administering MCMs. Robust “whole system” assessments are expected to be highly cost-effective considering the time and money required for R&D, acquisition, stockpiling, and maintenance of existing MCMs that may or may not be deliverable with current operational limitations. Similarly, the lack of adequate guidance for MCM use is a correctable deficiency that would be highly cost-effective. Specifically, the NPRSB recommends:

- 1) Utilizing the assessment results to establish an optimal MCM portfolio that considers the tradeoffs from each resource allocation
- 2) Incorporating cost-effectiveness analyses into decision making, and
- 3) Engaging the PHEMCE Enterprise Executive Committee (EEC) to refine the strategy for allocation of funds across agencies such that adequate resources are directed toward the highest priorities

**In conclusion, the NPRSB is highly encouraged by the initial trajectory but urges even greater prioritization and acceleration of comprehensive evaluations to assure that PHEMCE investments offer the greatest possible benefit to the US population.**

## Introduction

The National Preparedness and Response Board (NPRSB), formerly known as the National Biodefense Science Board (NBSB), provides recommendations, through the Department of Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response (ASPR) and the HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), to the HHS Secretary on strategic preparedness relevant to particular threats and/or medical countermeasure (MCM) needs.

The PHEMCE is an interagency coordinating body, chaired by the HHS ASPR, and its membership includes the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), the Food and Drug Administration (FDA), and interagency partners at the Departments of Veterans Affairs (VA), Defense (DOD), Homeland Security (DHS), and Agriculture (USDA). The PHEMCE coordinates the development, acquisition, stockpiling, distribution and use of medical products needed to mitigate a variety of potential high-consequence public health emergencies.

On May 22, 2013, the ASPR tasked the NBSB to make recommendations regarding methods and processes to define realistic goals for preparedness that consider the diverse needs posed by various threat scenarios. These goals were intended to inform the development, acquisition, and deployment of critical resources within HHS. As part of the task, the NBSB was asked to define an acceptable level of preparedness in light of operational and fiscal limits.

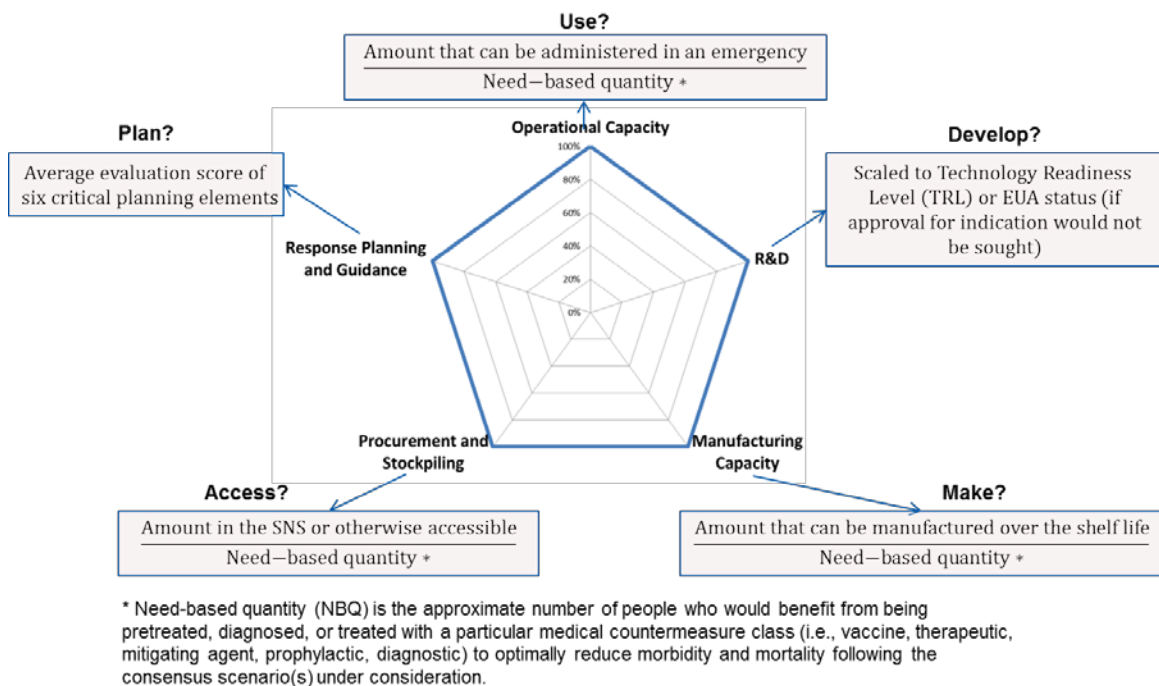
On January 10, 2014, the NBSB presented a set of recommendations for defining preparedness goals for chemical, biological, radiological, and nuclear (CBRN) threats as well as pandemics. The recommendations of the NBSB to the ASPR included the following text:

The NBSB recommends a broad characterization of preparedness and a whole-systems approach to goal-setting. The components of preparedness should include the various materials for use in a response, such as those procured for the U.S. Strategic National Stockpile (SNS), or held in sufficient quantity by commercial sources. Surveillance capability is required to know when and where these materials are needed. An effective planning system must be included to test preparedness strategies. An infrastructure is required to distribute them. Public and private resources are needed to use them effectively. Industrial capacity is required to resupply. The NBSB recommends that all material, infrastructure, and human components of preparedness be considered as an integrated and effective system.

The NBSB made these recommendations with the understanding that the nation's health security is closely tied to the availability and effective deployment of MCMs. Deficiencies in any single aspect of the PHEMCE could compromise the entire endeavor, so a "whole-systems" approach to review the enterprise is required. In other words, an MCM is only useful if it is needed, available, delivered, and appropriately administered within the timeframe that offers efficacy. **Thus, the NBSB's recommendation was based on the critical and urgent need to define specific gaps that limit the entire PHEMCE's effort.** Defining these gaps will maximize both the PHEMCE's effectiveness and its cost-effectiveness, as resources can be allocated to acute needs and away from interventions that are unlikely to benefit affected populations.

## “Whole-Systems” MCM Preparedness Assessment Approach

In response to the NBSB recommendation, PHEMCE experts designed an MCM preparedness assessment approach and performed a series of pilots using existing data relevant to specific threats. Inherent to the whole-systems approach is the concept that deficiencies in any single aspect of the system can function as bottlenecks, which compromise the value of a given MCM. The MCM preparedness assessment approach developed by the PHEMCE utilized five key metrics, each normalized on a scale of 1-100 on a spider chart (Figure 1).



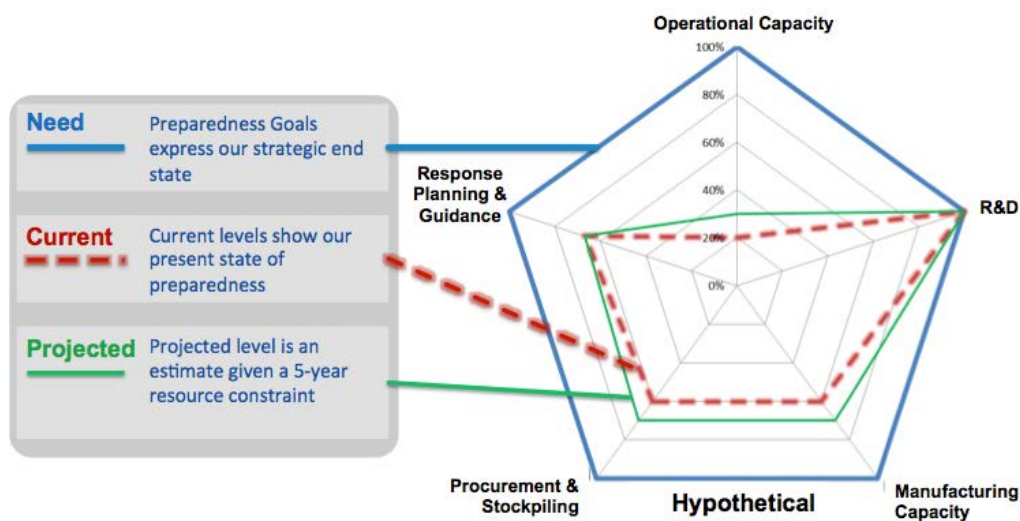
**Figure 1.** Spider chart of the five key metrics utilized to assess preparedness across the entire PHEMCE for an individual MCM.

The five metrics are outlined below:

1. *Research and development* was scaled using the Integrated Technology Readiness Levels (TRL) developed by the PHEMCE, with Level 1 being the lowest and Level 9 the highest. A maximum score is achieved when the specific MCM has achieved regulatory approval or can be used under an Emergency Use Authorization (EUA).
2. *Manufacturing capacity* assessed the point at which manufacturers reach steady-state between product creation and product depletion due to expiration (or use), normalized to the overall Need-Based Quantity (NBQ) identified in the Scenario Based Analysis. NBQ is the approximate number of people who would benefit from being treated with a particular medical countermeasure class to optimally reduce morbidity and mortality following the consensus scenario(s) under consideration.
3. *Procurement and stockpiling* assessed the amount in the SNS or availability through other means divided by the NBQ.

4. *Response planning and guidance* was assessed based on six critical planning elements: 1) MCM response strategy, 2) receiving, distribution, and dispensing guidance, 3) communication, public messages, and patient education guidance, 4) medical management guidance, 5) clinical utilization guidance, and 6) monitoring and adverse event reporting guidance. Each of the elements was evaluated for planning and training and two (MCM response strategy and monitoring and adverse event reporting) were also evaluated for exercising. A 5-level semi-quantitative score was used (very early, 0%; early, 25%; intermediate, 50%; established, 75%; and advanced, 100%) and these were averaged to produce the final score. Maximum scores indicate that all documentation is in place and there has been credible demonstration of the planning elements via some type of exercise.
5. *Operational capacity* assessed the numbers of courses of MCM that could be effectively administered in an emergency (based upon scenario-related capacities of those who would be responsible for administration) divided by the NBQ. The operational capacity score accounts for components of staffing, space, and supply information at the point of patient care. A maximum score indicates that all elements are available to treat the total number of anticipated cases.

For each pilot, a spider chart was generated to display the status of each key metric as of today and the anticipated status in 5 years given current funding (Figure 2).



**Figure 2.** A hypothetical status of an MCM showing readiness today, projected 5 years from now, and the level of needed preparedness.

SMEs from the PHEMCE Integrated Program Teams (IPTs) then performed four pilot assessments with assistance from ASPR staff. The assessments generated estimates of current and future preparedness levels across each metric as well as a set of priority activities to fill strategic gaps identified by this process. The specific MCMs assessed in these pilots were: 1) oral solid anthrax post-exposure prophylaxis antibiotics, 2) botulinum antitoxin, 3) meropenem for the treatment of *Burkholderia pseudomallei* and *B. mallei*, and 4) Prussian blue for treatment of internal radio-caesium contamination.

On February 17, 2016, the ASPR issued a task order to the NPRSB requesting a review of the “whole-systems” approach outlined above and of the initial pilots. The task order included three questions:

1. *Have we effectively implemented the preparedness assessment process in our pilot studies, particularly with regard to utilization of appropriate assumptions and data sources surrounding the operational capacity to use MCMs?*
2. *Did the preparedness assessment pilots appropriately evaluate current MCM capabilities, and remaining gaps, across the principal components of MCM preparedness?*
3. *How can we most effectively utilize the results of the preparedness assessments to inform decisions on future investments in MCM preparedness?*

On May 26, 2016 the NPRSB accepted the task order. A response to each of the three questions within the task order is included below.

**Task Question 1: Have we effectively implemented the preparedness assessment process in our pilot studies, particularly with regard to utilization of appropriate assumptions and data sources surrounding the operational capacity to use MCMs?**

To better understand the preparedness assessment process, representatives from the Office of the ASPR provided a briefing that outlined the process and key findings from the four pilots. The pilot MCMs were selected to capture different types of threats (*i.e.*, biological, chemical, and radiological) and different methods of administration (*i.e.*, oral and intravenous). According to that briefing, estimates of the NBQ and scores for each of the five key metrics were derived from a broad set of data sources and SMEs (Appendix 1). Existing additional data sources that could have informed these assessments appear not to have been used.

**The Office of the ASPR and other participating agencies are to be commended for undertaking this effort and for the collaboration across agencies that was necessary to establish a pilot process.** The resulting pilots represent the first attempt to link assessments across the entire PHEMCE, depend on critical insights from multiple different agencies, utilize SMEs both within and outside the PHEMCE, and have the potential to highlight critical gaps that would not otherwise be apparent. **However, our overarching observation is that the assessment process does not reflect the urgency that the NPRSB believes is needed to rapidly achieve a comprehensive understanding of our preparedness across threats.**

The NPRSB has the following suggestions for how to advance the existing assessment process in order to increase both the robustness and effectiveness of critical gap identification.

1) *Incorporate appropriate modeling that captures a range of uncertainties.* There are many unknowns in the field of CBRN threats, so an effective assessment approach must be broad in scope and extremely flexible, capturing a diverse range of scenarios that differ in size, impact, populations affected, location(s), and other factors (e.g., weather). In the pilot assessment of Prussian blue, two separate spider charts were generated with and without assumptions regarding availability of a diagnostic. This represents an example of modeling multiple different scenarios. However, the other assessments utilized fixed scenarios with “deterministic” numbers and averages to inform the assessments. In the absence of sensitivity analyses for the assessment model parameters, current assumptions drove the results of the assessments. For example, 20% hospital bed availability (the upper-bound) was used rather than a range, and staff absenteeism was not incorporated into assumptions.

Many of the current calculations also assumed linearity (e.g., in the determination of hourly throughput at points of delivery or the number of physicians needed in hospital care). Average time may incorrectly estimate overall resource needs, especially for care services. In actuality, there are differences in hourly throughput, and thus there will be different operational needs and resource usage across time and sites.

A computerized system model designed to understand interdependencies within the system, top-down and bottom-up, is critical. **The NPRSB strongly supports the rapid inclusion of computer-based modeling within the assessments to capture uncertainties rather than a fixed scenario-based assessment.** This modeling would provide a more robust dataset across assumptions and would allow for the inclusion of additional factors that may drastically affect MCM utilization (e.g. diversion of operational resources toward the “worried well”, healthcare worker absenteeism). This type of modeling is now commonly utilized in both academia and the private sector to better inform decision makers who face complex scenarios with significant uncertainties. A discussion and examples of how modeling could be applied to better inform PHEMCE-wide assessments are outlined in Appendix 2.

2) *Perform hands-on exercises to test the validity and shortcomings of model predictions.* In 2010, the U.S. government conducted a large-scale tabletop exercise called Dark Zephyr of an anthrax attack. The exercise employed participants from multiple layers of local, state and federal agencies and involved participants with a wide array of expertise. Performing an exercise of this scope and magnitude for every threat scenario requiring an MCM would be highly resource intense. However, some form of exercise that builds on the computer-based modeling should be conducted for each MCM. The extent to which these exercises range from “table-top” to “full-scale” should be decided based on threat priority and expected value. Exercises should require use of the full spectrum of extant MCMs, include mass casualty triage with point-of-care diagnostics (where applicable), and mock the administration of therapeutics and prophylactic treatments to the affected population (including children and other at-risk populations). Of great importance, the results from each exercise should be used to inform assessment parameters and help validate (or challenge) computer model-based predictions. It is essential to know how results from exercises diverge from computer-based assessments in order to refine the assessment methodology across multiple different threats, improve responses, and most efficiently deploy resources.

3) *Vet the updated assessment approach through a more extensive panel of SMEs, including experts in modeling and sensitivity analysis.* Although the NPRSB includes a diverse group of scientists, clinicians, administrators, public health experts, and academics, it does not necessarily have the appropriate breadth of expertise to robustly analyze the scientific merits of the assessment approach or the validity of each pilot study. Such analyses are better tasked to groups with deeper subject matter expertise such as those convened under the auspices of the National Academy of Sciences.

## **Task Question 2: Did the preparedness assessment pilots appropriately evaluate current MCM capabilities and remaining gaps across the principal components of MCM preparedness?**

The pilot studies focused upon threat agents identified by the Department of Homeland Security’s Material Threat Assessments (MTA). As stated above, the initial four pilots successfully interrogated each of the five key areas to provide a PHEMCE-wide assessment for each MCM. **This was a significant accomplishment, as it required the contribution of SMEs and capabilities across multiple agencies.** The NPRSB strongly encourages the PHEMCE to build on this momentum by designating additional

resources to perform more extensive assessments using the process outlined above. **The rapid application of this process across a range of MCMs is critical for informing the appropriate allocation of PHEMCE resources.**

Building upon the successful completion of the four pilots, the NPRSB has the following suggestions for future assessments across individual MCMs or threats.

1) *Perform assessments that incorporate the use of multiple MCMs when applicable for the same event.* As an example, the scenario examining an attack with *Bacillus anthracis* spores only assessed use of anthrax post-exposure antibiotics. Depending on estimated exposure levels, however, the recommended response combine both oral antibiotics and anthrax vaccine adsorbed (AVA). Similarly, in the pilot for *B. mallei* and *B. pseudomallei*, meropenem was selected for use in the first intensive stage of treatment for both of these infections because this antibiotic is a first-line therapy and included in the SNS. Another first-line treatment for *B. pseudomallei*, imipenem, was not included even though there is a large supply in the community. Other agents, including ceftriaxone, may be applicable in certain settings as well. In order to identify the key gaps, it is essential that real-world practice be incorporated into the pilots. In the absence of these additional agents, it is unclear whether the initial pilots accurately assessed current MCM capabilities and remaining gaps.

2) *Model permutations to determine how targeted interventions could improve PHEMCE effectiveness.* The computer-based modeling outlined in the response to Question #1 can be further utilized to establish the effects of hypothetical interventions on each aspect of the PHEMCE-wide effort. These interventions could include the introduction of different drug formulations, advanced MCM distribution strategies (e.g., user-managed inventory), or a rapid triage approach to screen MCM recipients. Computer modeling can also identify critical gaps that emerge during multiple concurrent attacks (i.e. multiple sites and/or sources). Modeling permutations is essential to understand whether “trade-space” can be identified and inform targeted advancements in preparedness that maximize overall impact.

3) *Engage additional stakeholders, including states and localities, the private sector, and non-profit organizations, to design and perform meaningful exercises that inform the current gaps in operational capacity and inform the design of accurate models.* The pilot studies appeared to be scientifically robust on the key metrics of Research and Development, Manufacturing, and Stockpiling. In contrast, the Response Planning and Guidance determinant used a standardized, although non-validated, assessment tool. The Operational Capacity determinant for all but the anthrax pilot, which assessed high operational readiness, relied on many assumptions regarding delivery to the patient. Although the CDC’s Division of State and Local Readiness data and Bureau of Labor for health-care provider estimates were used to help inform this determinant, this element appears the least robust. In general, the assumptions were not informed by data that could have been supplied by partners such as local and state health departments, hospitals, and community emergency response teams. Hence, it is possible that the operational evaluation scores have a higher degree of uncertainty than the other key metrics. The most accurate assessment of PHEMCE effectiveness requires that the “whole-systems” include both horizontal (i.e., interagency) and vertical (i.e., other areas of government and non-governmental stakeholders) dimensions.

4) *Submit assessments for review to panels of governmental and non-governmental SMEs.* Ideally, there should be a review of each assessment by SMEs from outside agencies, business, and academia. These reviewers would include a detailed evaluation of the methodology, assumptions, data sources, and



conclusions. Reviews should be utilized to iteratively inform the refinement of subsequent assessments, computer-based models, and exercises.

### **Task Question 3: How can we most effectively utilize the results of the preparedness assessments to inform decisions on future investments in MCM preparedness?**

The NPRSB recognizes that careful and informed decisions are essential for maximizing the extent of preparedness that can be achieved with finite resources. The key lessons learned from the “whole-systems” preparedness assessments should be the scientific foundation for future investment in MCM preparedness, which makes it imperative that these assessments are both robust and valid. Iterative assessments of preparedness should guide the balance between dollars spent to stockpile MCMs, develop additional novel MCMs, provide guidance on the use of MCMs, and establish and coordinate operational capacity for administering MCMs.

**The NPRSB believes that the adequate resourcing of “whole-systems” assessments is strategically essential to efficiently address future threats, even if it compromises funding to other aspects of the PHEMCE.** This resourcing would be highly cost-effective compared to the very high costs of R&D and stockpiling of agents that lack optimal guidance and operational capacity building. As an example, recent modeling performed by PHEMCE experts (Ajao et al. DMPHP 2015) demonstrated that 26,000-56,000 additional ventilators could be utilized by hospitals across the nation in the event of a nationwide influenza emergency. The factor that prevented further expansion of that number was the inadequate availability of trained staff. As a result of this modeling, the SNS ventilator stockpile will be limited to a range consistent with operational capacity for utilization. Thus, rather than purchasing ventilators that would never be utilized, the financial resources will be applied to address other critical gaps. This modeling also guides evaluation of alternative costs and opportunities, such as the development of easier-to-use ventilators or the training of additional professionals to manage ventilated patients during crises.

The interagency nature of the PHEMCE is uniquely suited to support complex modeling across all five key aspects and thereby inform decisions that maximize PHEMCE effectiveness. However, it remains unclear to the NPRSB whether findings from that modeling will drive changes in resource allocation from one agency’s purview to another’s. The NPRSB has the following suggestions for how to utilize results from the assessments to inform decisions on future investments in MCM preparedness:

- 1) *Utilize the assessment results to establish an optimal MCM portfolio that considers the tradeoffs from each resource allocation.* The PHEMCE represents an extremely diverse range of capabilities and investments. There is not going to be a single plan that satisfies all objectives because the risks/threats are diverse and resources are finite. Hence, understanding tradeoffs becomes critical for decision-making. An “efficient frontier” is a term from portfolio theory that describes the optimal portfolio based on return with an acceptable level of risk. Establishing such a frontier would allow the Enterprise Executive Committee (EEC) to consider how targeted expenditures would be predicted to improve overall PHEMCE performance. This efficient frontier would be informed by individual assessments of each threat, including exercises that incorporate multiple MCMs and real-world practice. At the same time, computer-based modeling that tests the effects from hypothetical threats and alternative interventions (such as a non-IV MCM formulation) can be used to estimate the potential value of a targeted investment.

2) *Incorporate cost-effectiveness analyses into decision-making.* The cost-effectiveness of tradeoffs is an essential component of decision-making that has not yet been incorporated within the PHEMCE assessments but should help drive responses to the modeling. For example, the delivery of MCMs will be significantly compromised if local practitioners and public health representatives are not informed about the appropriate use of MCMs. Thus, efforts to maximize population readiness, preparedness training, and just-in-time education (e.g., through playbooks and medical guidance) are extremely cost-effective compared to the R&D and purchasing costs for MCMs, which are unlikely to be appropriately utilized in the absence of that education and training.

3) *Engage the EEC in developing a strategy for allocation of funds across agencies to address critical gaps.* The PHEMCE has a robust process for periodic revisions of its strategy and implementation plans that provides an opportunity to make corrections and updates to the plan. The key lessons from the MCM evaluation reviews should be formulated into recommendations by the PHEMCE experts and promptly sent to the EEC to guide an informed decision-making process. Budget allocations and/or responsibilities should be shifted across agencies to ensure that sufficient resources are available to address critical gaps in a timely manner.

**Appendix 1:** Data sources and SME categories utilized to inform estimates of the NBQ and each of the five key metrics.

- **Need-Based Quantity (NBQ)**
  - Scenario-Based Analysis Requirements
- **Research and Development**
  - PHEMCE Portfolio Tracking Tool for Technology Readiness Levels (TRLs)
  - IPT SMEs
- **Manufacturing Capacity**
  - IPT SMEs
- **Procurement and Stockpiling**
  - SNS Annual Review
  - CDC/OPHPR/DSNS7
  - IPT SMEs
- **Response Planning and Guidance**
  - ASPR, CDC/OPHPR/DSNS and DSLR, DHS/FEMA, and IPT SMEs
- **Operational Capacity**
  - Prior assessment for similar routes of administration
  - CDC/OPHPR/DSLR (Operational Readiness Review Tool)
  - IPT and operational SMEs
  - Integrated Capability Document requirements chapters and annexes

## **Appendix 2:** Rationale for and applications of mathematical modeling

It is difficult to predict how effective a response will be to an event that is either man-made (e.g., CBRN), or natural (e.g., pandemic influenza). However, by defining a range of probable sizes, locations, and conditions for the event, it is possible to develop mathematical models that examine the effects of interventions on key outcomes. These models take into account important variables that may be interconnected in producing the desired outcome, such as the amount of an MCM that is available and the ease of its administration. It is then possible to assign a likelihood that each of the interconnecting responses can and will occur (as noted in the example below) and thereby achieve a prediction whether, for any given scenario, the public health response will be successful.

Using a previous full-scale exercise (Dark Zephyr) as an example, we can plan a complete public health response for an aerosol exposure to anthrax. By postulating an exposure of a certain magnitude of anthrax (e.g., 1 kg) over San Francisco at a certain altitude, the spread of anthrax spores across the region can be predicted based on prevailing wind patterns. From this exposure prediction, the number of adults and children who are likely to need treatment can be predicted and the needs for an appropriate public health emergency response can be calculated. The number of doses of antibiotics and vaccines needed to respond can be assessed (and stockpiled or available from local resources). A plan can be created to get these needed MCMs to those exposed. The plan would include, for example, the number and character of drug dispensing locations and number of personnel required to dispense medications with the expectation of a response within hours after detection of the event. Clinic, hospital, equipment, and personnel needs can be predicted for each type of event, size of event, and location of event. Each component needed to insure an overall successful response can be assigned a likelihood of being achieved. Well-recognized software programs (such as those that perform Monte Carlo simulations) can combine all of these independent components of the required public health response together (the “whole-systems” response) to arrive at a single point-estimate likelihood of success with variability of each and every assumption assigned for each part of the interconnecting response.

If one part of the response improves over time (e.g., increased availability of hospital beds that would be needed for the response), then the program can easily be re-run, and the updated likelihood of achieving success can be demonstrated. The various assessments of readiness can be made at any time, and the program can assess the current, probabilistic likelihood of success. Critically, one can examine the impact of each interconnecting part (clinics, personnel, medications, etc.), on the overall likelihood of success, so that specific resources can be targeted to interventions that offer the greatest increase in the likelihood of overall success. In this way, it is possible to identify the components and create methods and processes that can define realistic goals for preparedness.

An example of this type of complex interconnectedness is captured in the decision-tree analysis below (Figure 3). This type of analysis captures potential uncertainties in each of the dimensions. In this approach, uncertainties are allowed along the paths of the five dimensions. Hence, different probabilistic effects can inform our understanding of what eventual capability we have or we do not have. In the Figure we show just one layer -- the uncertainty in assessment at each dimension and the ultimate probability of success along each potential path. For a two-layer approach, one can first designate the assessment percentage for each dimension (from the spider chart) and then, within each assessment, introduce the uncertainty. This two-layer approach results in a compounded tree with dimension assessment overlaid with a range of uncertainties.

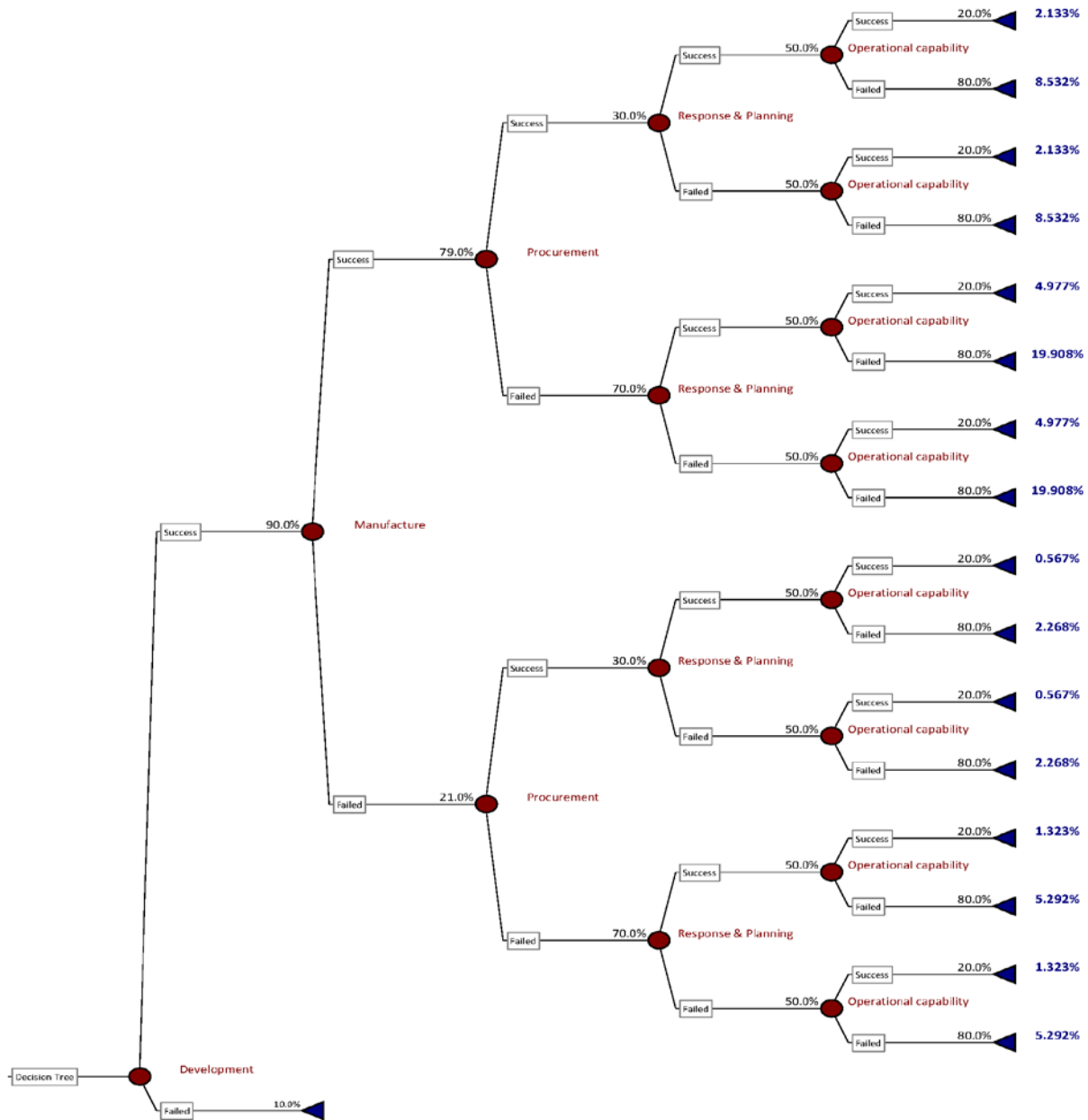
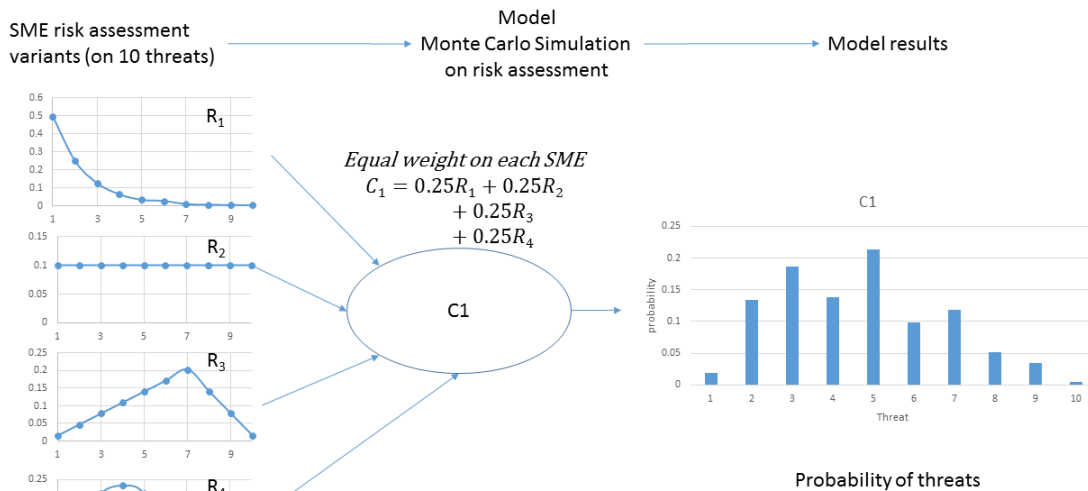


Figure 3. The figure above is an example of a decision-tree analysis.

In the alternate strategy depicted below, four SMEs assigned risks of 10 different threats (for example, R1-R4 describing the likelihood of type, size, location, impact of each threat). The variability demonstrated by the combination of the four SME assessments (assuming each SME opinion is equally valuable) can be statistically evaluated (modeled) to create an averaged assessment of probability of each of the threats. These assessments can be used in multiple ways. First, they can be incorporated within a portfolio investment optimization model (Figure 4) to determine MCM stockpile combination, strategies for response, operational capacities, and capability development. Policy makers can contrast results to understand tradeoffs in their decision-making. Second, they can be further combined statistically with a calculated likelihood of a successful response to each of the threats based on current or proposed availability of all required resources for each threat.



**Figure 4.** The figure above is an example of an MCM portfolio investment optimization model.