NBSB National Biodefense Science Board

Medical Countermeasure Research and Development Goals to Prevent Infectious Disease Epidemics

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DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

ASPR
ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

Medical Countermeasure Research and Development Goals to Prevent Infectious Disease Epidemics

The All-Hazards Science Response Working Group of the National Biodefense Science Board (NBSB) initiated discussions on this topic in the fall of 2019 and completed this White Paper in the first quarter of 2020. The Coronavirus Disease 2019 (COVID-19) pandemic has occurred during the drafting of this White Paper. Since the Recommendations in this White Paper remain valid and timely implementation could help in future outbreaks, the NBSB has decided to release it.

To accelerate research and develop goals to prevent infectious diseases disasters, the NBSB recommends the following, not in order of priority:

Recommendation #1. Continue to strengthen the Department of Health and Human Services (HHS) capacities to identify potential Disease X events anywhere in the world with additional support for implementation of bio-surveillance platforms, international capacity building, and open-source surveillance.

Example benchmarks:

- Written comprehensive, national bio-surveillance strategy that includes international sources
- Assignment of reporting and analytic responsibilities with decision-support tools
- Written comprehensive global health security strategy that complements the National Health Security Strategy

Recommendation #2. Increase or expand resources for enhanced health diplomacy and other mechanisms (such as deployable teams) that quickly engage governments and health authorities at the highest levels where sentinel events occur to:

- Gain faster access to critical information
- Collaborate on modeling and assessment of triggers for subsequent actions
- Support acquisition and sharing of pathogen isolates and patient samples

Example benchmarks:

- Complete comprehensive analysis and decision matrix for each event within 7 days of detection anywhere in the world;
- Decide immediately to begin targeted Medical Countermeasure (MCM) development when indicated by threat analysis or modeling
- Create support for an international framework for sample sharing during a crisis

Recommendation #3. Support or expand development of mechanisms/systems to:

- Enhance and promote the sharing of pathogen genetic sequence information as soon as known, within the international science and public health communities (e.g., World Health Organization)
- Transport specimens containing active pathogen to predesignated centers for MCM and diagnostic development

Example benchmark: acquisition of needed biological material soon after recognition of a potential crisis

Recommendation #4. Establish or expand an effort to develop pre-approved clinical trial protocols in the United States and train an appropriate number of staff to support "field trials" of new or repurposed MCMs (i.e., vaccine or therapeutic) at the same time administered to at-risk populations.

Example benchmarks:

- Draft a national "field trial" protocol that has been vetted with relevant stakeholders, reviewed and pre-approved by an appropriate Institutional Review Board
- Exercise trial protocols for several types of MCM and field trial settings
- Promote drafting of preapproved minimal requirement guidelines for manufacture and use for clinical test materials

Recommendation #5. Formalize plans to activate Operation Centers and R&D Facilities, and establish an appropriate chain of command / task force structure to rapidly launch and continue to coordinate the MCM development/deployment pathways.

Example benchmarks:

- Activation of the HHS Secretary's Operation Center (at least Level II) on the day that a threat analysis is completed (i.e., by at least day 7 following detection of a potential crisis)
- Hold stakeholder meetings for the needed coordination teams within 48 hours of activation of the HHS Secretary's Operation Center

Recommendation #6. Fund and conduct emergency planning for MCM development and conduct workshops and/or exercises to enable response in the following areas:

- Develop and deploy diagnostics in 14 days or less.
  Example benchmark: deployment of diagnostic for trials to enable use under an Emergency Use Authorization (EUA) from the Food and Drug Administration (FDA)
- Develop and deploy an experimental therapeutic(s) in 28 days or less.
  Example benchmark: inventory of available resources to enable initiation of a clinical trial

- Develop and deploy an experimental vaccine(s) in 28 days or less
  Example benchmark: inventory of available resources to enable initiation of a clinical trial

Recommendation #7. Formulate and coordinate a secure infrastructure plan within the United States biomedical and healthcare sectors that ensures that the needed facilities (including manufacturing, healthcare, distribution sites) are ready (i.e., maintain a "warm base") to quickly achieve full scale.

Example benchmarks:
- Complete a functional exercise for each facility demonstrating its ability to meet goals within 7 days of a warning indicator
- Develop a resource inventory
- Evaluate national points of distribution

Recommendation #8. Establish or expand mechanisms for rapid access to an emergency response fund to enable MCM develop and deployment.

Example benchmarks:
- Confirmation of available funding in reserve
- Appropriation language that has been pre-approved by Office of Management and Budget and Congressional staff

Recommendation #9. Establish a task force to develop a national strategy to reduce "vaccine hesitancy", with additional focus on anticipating acceptance of a novel drug or vaccine in the event of a major infectious disease threat.

Example benchmarks:
- Increased acceptance of routine vaccination as indicated by standard surveys
- Positive results from focus groups and stakeholder engagements with community-based organizations

Appendix 1

NBSB considered the scientific and operational challenges to accelerating the development and deployment of emergency MCM – therapeutic drugs, vaccines, personal protective equipment, and diagnostic tests – to improve responses to a potentially catastrophic infectious disease epidemic. In 2018, the WHO listed "Disease X" as a priority pathogen for MCM research and development (R&D) because of the ongoing potential for emergence of novel pathogens with devastating effects.[*] Whether naturally occurring or as the result of laboratory manipulation, Disease X is characterized, for the purposes of these recommendations, as having high transmissibility (reproductive rate of 3-10 cases per case or more) and a high mortality rate (case fatality rate of 30% or more), similar to smallpox, with asymptomatic incubation period that is long enough to allow for some exposed individuals to transmit the infection to others at locations far from the original source. In a matter of weeks, millions of lives would be at risk.

In the Disease X scenario considered by NBSB, there are no diagnostic tests, therapeutic treatments, or vaccines available at the onset of the outbreak; the pathogen is already widespread when the outbreak is recognized. Rapid administration of MCM would be required to control the epidemic and preserve the normal functions of society. While social distancing and the use of non-pharmaceutical interventions (basic measures to minimize the spread of germs, such as handwashing, covering mouth when coughing or sneezing and use of negative pressure rooms for patients hospitalized with Disease X) will be immediately critical to slow the course of the epidemic, NBSB advises that rapid deployment of vaccines is the most effective way to contain transmission and prevent the majority of deaths[†]. Current programs in HHS, in particular the National Institutes of Health, National Institute of Allergies and Infections Disease, the Centers for Disease Control and Prevention, the Biomedical Advanced Research and Development Authority (BARDA), and the U.S. Food and Drug Administration, and the Department of Defense have had many important advances recently in their support for and collaborations with private and public institutions. NBSB recognizes that these collaborations have been effective at pushing forward the leading edge of new technologies. While the responses to Ebola virus outbreaks between 2014 and 2018 and the response to the 2019 novel

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[*] World Health Organization (WHO). 2018 Annual review of diseases prioritized under the Research and Development Blueprint: Informal consultation, 6-7 February 2018. Online at 2018 Annual review of diseases prioritized under the Research and Development Blueprint. Last accessed 27 January 2020.

[†] Matrajt L, Halloran ME, Longini IM Jr. Optimal vaccine allocation for the early mitigation of pandemic influenza. PLoS Comput Biol. 2013;9(3):e1002964. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3605056/ (accessed 30 November 2019).

[†] Matrajt L Jr, Longini IM. Optimizing Vaccine Allocation at Different Points in Time during an Epidemic. PLoS One. 2010 Nov 11;5(11):e13767. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2978681/ (accessed 30 November 2019).

coronavirus indicate significant improvements compared to prior eras of emerging infectious disease response, NBSB recommends, that HHS continue improving toward achieving aspirational goals in the near future. Aiming at aspirational goals increases the likelihood that an agile and effective infectious disease response against Disease X and other types of lethal biological threats will be available when needed.

NBSB advises HHS to consider several overarching themes:

- R&D for technologies, platforms, and systems to develop new MCM against Disease X in 28 days from the recognition of the outbreak, which NBSB recommends as target timeline, requires new incentives, specific goals, and advanced planning within HHS (involving many stakeholders) to achieve effective capabilities.

- Centralized coordination of pre-established collaborators optimizes the contributions from all partners, leveraging funding from the federal government, to analyze surveillance data, share resources, and conduct a predefined sequence of actions to reach MCM development targets.

- Advanced medical readiness should parallel development of new MCM capabilities, including exercising plans to implement non-pharmaceutical interventions against Disease X while concurrently preparing for MCM administration (whether population-based or targeted).

- Advanced medical readiness should include preparing to invoke emergency use authorizations (EUA) and field trial protocols for successive iterations of MCM.

- During the response to Disease X, use a continuous risk-benefit analysis and a well-defined utilization, allocation, and clinical guidance strategy to maximize public safety and MCM utility.

- An accelerated MCM development strategy requires:

    - Diagnostics development at predesignated centers that have access to non-inactivated isolates followed by rapid field testing, manufacturing, and distribution of validated modules for point-of-care diagnostics, rapid screening, and confirmatory diagnostics.

    - Vaccine development at predesignated centers with validated or pre-qualified technologies/platforms, raw material resources, and scalable manufacturing that can rapidly begin parallel selection and testing of multiple vaccine candidates.

    - Drug development and repurposing approved drugs at predesignated, Biosafety Level (BSL)-4 centers that can conduct massive parallel screening of existing

antivirals while other centers initiate small molecule design and testing *in vitro* and/or development of therapeutic monoclonal or polyclonal antibodies.

Specific Challenges and Related Recommendations:

- **Early Detection and Identification of Pathogens.** Delays in recognition of a potentially serious outbreak and characterization of the pathogen reduce the amount of time available to develop effective MCM. It is critical that HHS continue to advance development of technologies and partnerships to support characterization of novel pathogens and logistics support for sample transfer. Close coordination with the World Health Organization (WHO) will be necessary. *(Recommendations 1-3)*

- **Early Activation of HHS MCM Coordination Mechanisms.** Similar to "normal" responses under Emergency Support Function-8, an immediate whole-of government and whole-of-nation approach to MCM development requires centralized management by HHS to optimize efficiency and speed of the MCM pathways. Delays in coordination due to political or financial concerns, lack of organizational readiness, lack of transparency, and uncoordinated communication will cause critical – and avoidable -- delays. *(Recommendations 4-5)*

- **Rapid Launch and Coordination of MCM Development Pathways.** Immediate coordination between the government and industry partners will increase the potential for success of parallel efforts to produce the best possible MCM. Such coordination includes collection of data in near real-time to support regulatory decisions, rapidly identifying the most promising MCM candidates and directing/redirecting efforts to ensure production at an appropriate scale, and simultaneous approval for clinical trial protocols under appropriate regulatory approvals that ensure collection of additional efficacy and side-effect data during administration of the MCM. *(Recommendation 6)*

- **Adequate Infrastructure, Material, and Emergency Funding:** Development of MCM for an unknown, highly virulent pathogen in sufficient quantities to be effective at the population level requires specialized facilities, appropriate material, distribution systems, and sufficient funding. Such resources would include, among other things, predesignated laboratories with expansive biosafety level (BSL)-4 capacity, qualified raw materials, and trained laboratory, clinical, and security personnel. *(Recommendations 7-8)*

- **Manage Public Trust**. Community cohesiveness and collective action will be critical to respond to a societal Disease X threat through acceptance of novel MCM. Heightened hesitancy to abide by routine vaccination recommendations, public distrust of vaccines, miscommunications and rumors regarding the risk of illness compared to the risk of side effects, and active defiance can defeat the national response strategy. *(Recommendation 9)*

Appendix 2: Speaker Presentations

June 11-12, 2019

- **Exploring Issues in Biodefencse Science: Rapid Development of Vaccinces and Other Biologics for Emerging Infectious Diseases**. *Gray Heppner, MD, FACP, FASTMH, Co-Chair of the All Hazards Working Group, CMO.*

September 11, 2019

- **Exploring Issues in Biodefense Science: Development and Use of Animal Models to Enhance Rapid Approval of Novel MCM**. *Elizabeth Leffel, PhD, MPH, Co-Chair of the All Hazards Science Working Group, President of Leffel Consulting Group, Inc.*

December 3-4, 2019

- **Anticipatory Modeling of Requirements for Emerging Infectious Diseases – Review of Gaps and Challenges to Respond to Eastern Equine Encephalitis Virus.** *CAPT Perdue, MD., Elizabeth Leffel, PhD, MPH, and Ms. Anna Tate, MPH, Requirements Division, SPPR, ASPR*

- **Strategic Considerations to Accelerate Development and Deployment of Vaccine for a High Consequence Emerging Infectious Diseases**. *Gray Heppner, MD, FACP, FASTMH, Co-Chair of the All Hazards Science Working Group; CMO of Crozet Biopharma LLC*

- **Preparedness for Emergency Infectious Diseases:**
  - **Review of Programs at the Department of the Interior.** *M. Camille Hopkins DVM, MS, PhD (ORCID), Wildlife Disease Coordinator, US Geologic Survey Ecosystems Mission Area*
  - **Perspectives from a practicing equine veterinarian.** *Megan Mathias, DVM, True North Equine (private practice)*
  - **Perspectives from a State Epidemiologist in an Outbreak State.** *Catherine M. Brown, DVM, MSc, MPH, State Epidemiologist and State Public Health Veterinarian, Bureau of Infectious Disease and Laboratory Sciences*

- **Focus on Issues Related International Sample Sharing**
  Collin Weinberger, MPH, Senior Global Health Officer, Office of Global Affairs, US Department of Health and Human Services

Appendix 3: NBSB Working Group (WG)

All Hazards Science Response WG Members:

- Elizabeth Leffel, PhD, MPH, AHSR Working Group Chair
- Donald Gray Heppner, MD, FACP, FASTMH, AHSR WG Co-Chair
- Prabhavathi Fernandes, PhD, NBSB Chair
- Noreen A. Hynes, MD, MPH
- Catherine Slemp, MD, MPH
- Tammy Spain, PHD

National Advisory Committees Staff:

- CAPT Christopher Perdue, MD, MPH, Designated Federal Official (DFO)
- Maxine Kellman, DVM, PhD, PMP, Alternate DFO
- Darrin Donato, MS, Domestic Policy Branch Chief
- LCDR Cliffon Smith, MPA
- Jose Velasco, MSW
- Mariam Haris, MPP