Optimizing Chemical Agent Medical Countermeasures in the Strategic National Stockpile

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Executive Summary: Chemical agents, unlike biological agents such as bacteria or viruses, include toxic chemicals that cause adverse effects such as death, temporary incapacitation, or permanent harm to humans or animals. These agents are structurally and functionally diverse, leading to a wide range of possible dangers. However, federal threat assessments over the years have deemed chemical agents a lesser threat than biological agents. This, in turn, has led the Department of Health and Human Services to deprioritize critical research and investment into the stockpiling of medical countermeasures (MCMs) that can save lives in the event of an exposure, resulting in lowered appropriation levels toward developing MCMs against chemical agents for the Strategic National Stockpile (SNS). Additionally, annual reviews of the SNS that directly inform budget allocations and appropriations for future years were not conducted from FY2017 to FY2019, further weakening SNS preparedness against chemical threat agents in a constantly changing threat landscape. As such, there are gaps in the inclusion and pursuit of medical countermeasures for chemical agents into the SNS. Costs for non-procurement spending, transitioning MCM integration, and maintaining repositories of existing MCMs from fiscal years (FYs) 2020 and 2021 were calculated based on planned spending costs for the SNS as published in Appendix A of the Public Health Emergency Medical Countermeasures Enterprise Multiyear Budget for FY18-22. The allocated SNS funding for FYs 2020 and 2021 combined is insufficient to maintain an updated repository of existing medical countermeasures to be drawn from in the case of a public health crisis while simultaneously growing to integrate newer countermeasures compared to planned spending for those years. As such, regulatory policies that enforce annual SNS reviews are recommended. Additionally, increased direct appropriations and bolstering alternative funding avenues for MCM development are essential for research and development of MCMs for emerging threats.

I. Background

The US Strategic National Stockpile (SNS) collects and maintains a repository of pharmaceutical medical countermeasures (MCMs) to protect the public in the case of a public health emergency in the United States caused by a chemical, biological, radiological, or nuclear (CBRN) threat. Every year, the Public Health Emergency Medical Countermeasure Enterprise (PHEMCE), an interagency group, is tasked with "identifying national health security needs and making recommendations" to the Secretary of Health and Human Services (HHS) about many aspects of the SNS, including research and development, procurement, and stockpiling (Gottron and Wyatt 2023, 2). Over the years, these assessments have

deemed chemical agents as less likely than biological agents to be weaponized or cause a public health emergency. This has led to HHS deprioritizing critical research and investment into the development and stockpiling of MCMs for chemical agents, resulting in significant gaps in their inclusion into the SNS along with a reduced pursuit of new, more effective MCMs (Neumeister and Gray 2021, 4). Although chemical agents are weighed to be a lesser threat than biological agents, many chemical agents and/or their byproducts have industrial applications and cannot be easily eliminated from general use. This makes any attempt at eradicating their threat level impossible.

The use of chemical weapons in 2013 devastated the Syrian population, resulting in over 1,000 deaths and injuring thousands more (Rosman et al. 2014, 2). Chemical agents such as chlorine gas have since been used repeatedly across Syria as recently as 2018 (D.o State 2023, 4). Additionally, nerve agents were used to poison Kim Jong-nam (half-brother of North Korean Supreme Leader Kim Jong-un) in 2017 and residents of Salisbury, UK in 2018. It is critical to optimize SNS preparedness for future chemical agent threats by (1) improving existing MCMs by addressing current shortcomings, and (2) developing novel MCMs for potential chemical threats lacking an FDA-approved antidote.

i. Improving existing MCMs by addressing current shortcomings

While some chemical agents do have FDA-approved MCMs, they can sometimes be insufficient to address all of the effects of a given chemical agent on the human body. For example, organophosphorus (OP) nerve agents are a class of chemical warfare agents that interfere with neurotransmission, leading to excessive muscle contractions, seizures, and eventually death. A reactivator is the only drug that can directly reverse the cause of OP intoxication. However, the only reactivator approved by the FDA has limited function against some OPs along with poor penetration of the brain, where an OP MCM would be optimally effective (Worek, Thiermann, and Wille 2020, 2278-2280 and Shih et al. 2011, 59). The search for a better MCM that addresses these shortcomings has been ongoing since but to no avail, though not for lack of effort. The relative deprioritization of chemical agent countermeasure development and resultant scaling of funding towards those efforts have added friction on the path to addressing shortcomings of existing MCMs. The availability of an MCM in and of itself cannot be considered satisfactory when the consequences of chemical weapon usage are so dire.

ii. Developing novel MCMs for potential chemical threats lacking an FDA-approved antidote

Unfortunately, the development of SNS-qualifying MCMs against non-OP chemical agents have lagged behind their OP counterparts due a combination of factors including the "dearth of knowledge of mechanisms of action, the difficulty of producing MCMs that function post-exposure, and the lower prioritization from the threat assessment process" (Neumeister and Gray 2021, 9). The weaponization of chlorine gas in 1915 during World War I was the first recorded use of chemical agents in warfare and was used as recently as 2018 in Syria. Chlorine was also categorized as the most common pulmonary irritant in the United States in 2016 per the American Association of Poison Control (Morim and Guldner 2022). The established toxicity of this chemical agent both on and off the battlefield highlights the impact of this threat on overall health security. The lack of an approved countermeasure for chlorine gas further underscores the need to continue to diversely invest in the research, development, and acquisition of novel MCMs that could save numerous lives.

Pharmaceutical-based agents (PBAs) such as fentanyl analogs and other synthetic opioids are newer to the chemical threat space but are just as toxic as OPs and chlorine gas. Efforts to understand the true threat that PBAs pose are ongoing, as they cause diverse effects such as sedation, dissociation, and short-term memory impairment (D.o State 2023, 8). In February 2022, a naloxone autoinjector received FDA approval for use by the military and first responders in both suspected and confirmed opioid exposure events (JPEO-CBRN 2022). However, per the Annual Condition (10)(C) Annual Report on Compliance with the Chemical Weapons Convention released by the US Department of State in April 2023, there are concerns about Russia, Iran, and China potentially pursuing the research and development of various PBAs for offensive purposes, in direct violation of the Chemical Weapons Convention (D.o State 2023, 8-10). These findings signal the need to be wary of the harm foreign

adversaries could pose to US public health security. It is, therefore, worth allocating more resources towards the development and stockpiling of MCMs against PBA chemical threats to protect the American public.

Lapses in federally-mandated reviews of the SNS and the effect of compounded relative deprioritization of chemical agents over time have collectively weakened preparedness against chemical agents. It is still worth investing in strengthening SNS preparedness against future chemical agent exposures and attacks to secure public health.

II. Budget Analysis

To better assess the current requirements to strengthen the SNS, fiscal data for FY2020 and FY2021 was obtained from the Administration for Strategic Preparedness and Response (ASPR) website and analyzed to inform the subsequent recommendations. All budget data was obtained from Appendix A of the Public Health Emergency Medical Countermeasures Enterprise Multiyear budget for FY18-22. Total costs for non-procurement spending ($485.7 million) and integration of transitioning MCMs from FDA approval to stockpiling ($881.6 million) were calculated based on planned spending costs for the SNS in FY2020 and FY2021 as published in Appendix A. The estimated cost for maintaining repositories of existing MCMs such as smallpox ($1.3 billion) was then calculated by subtracting the summed cost of non-procurement and transitioning MCMs from the combined total planned SNS spending for FY2020 and FY2021 ($2.7 billion). These costs were then compared to the sum of the allocated FY2020 and FY2021 SNS budgets ($1.3 billion). (DHHS 2019, 19-21).

There is a noteworthy difference between the planned spending for the SNS and funding allocated via direct appropriations (Figure 1). Specifically, an additional $1.4 billion is required on top of the combined allocated $1.3 billion budget of the SNS for FY2020 and FY2021 to accommodate planned non-procurement costs (operation, sustainment, and program support), integration of six new MCMs planned to transition from development during the same time period, and routine maintenance of existing MCMs.

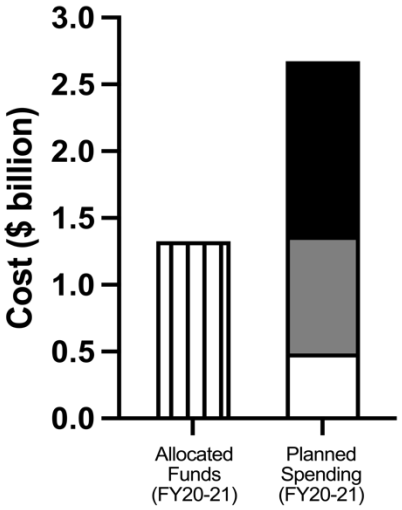

Figure 1: Side-by-side comparison of the sum of allocated FY2020 and FY2021 SNS budget (▥/striped, $1.3 billion) via direct appropriations compared to planned spending by the ASPR over the same time period ($2.7 billion). Planned spending costs for the SNS stacked by category: non-procurement (□/white, $485.7 million), integration of transitioning MCMs (▭/gray, $881.6 million), maintenance of existing MCMs (■/black, $1.3 billion).

The sluggish increases to the SNS budget over the past five years have clearly been insufficient to accommodate the requirements of the SNS. The significant disparity between the allocated SNS budget for FYs 2020 and 2021 compared to planned spending for the same time frame indicates that the direct appropriations alone do not offer enough support for the maintenance of existing MCMs, let alone cover costs for optimizing them. In order to keep the SNS afloat given the allocated funds, adjustments on its composition or logistical function likely have been made. Of note, only one of the six MCMs being integrated into the SNS is for a chemical agent, further illustrating the overall lower representation of chemical agent countermeasures in the SNS.

III. Policy Recommendations

As part of preparing for a national health emergency, it is essential that the composition of the Strategic National Stockpile be regularly monitored and updated to reflect the threats that chemical agents could pose to public health in real time. As such, the current mandate establishing the annual review should be revised. Recommendations stemming from a congressionally-mandated requirement

inform SNS funding and inventory decisions in the coming years, making this annual requirement a key component of sustaining the SNS. Details of the review process itself are generally guarded for operational security, but a congressional committee with the appropriate need-to-know could be established and act as a stringent enforcing authority to hold reviewers accountable. Lapses in this review requirement by the PHEMCE from FY2017 through FY2019 (Gottron and Wyatt 2023, 4) further weakened SNS preparedness against chemical agents in a constantly changing threat landscape. Had these reviews been conducted, perhaps they could have more accurately informed budget allocation and inventory decisions for the SNS in FY2020 through FY2022, which were all underfunded. As such, establishing mechanisms to hold PHEMCE accountable for conducting annual reviews of the SNS are necessary to avoid repeating the mistakes made in previous years.

Given that the allocated budget for the SNS in FY2020-2021 was insufficient to cover the costs associated with maintaining the SNS as planned, as seen in Figure 1, the resultant funding shortage is preventing the SNS from fulfilling its role as a vital repository that could be drawn upon in the case of an emergency. Increasing the budget allocation for the SNS via direct appropriations by $1.5 billion would allow for adequate resources to cover routine non-procurement costs and maintenance of stocks of available MCMs, while also allowing for the integration of MCMs transition from development into stockpiling at a level approximately equal to the planned spending level by the ASPR for FYs 2020 and 2021. Unfortunately, this task is easier said than done. Achieving this proposed increase would require a majority and bipartisan support in Congress, and convincing them of the value in funding preparedness efforts for events that may never occur would be especially challenging. The current political climate also makes selling the idea of increasing federal spending and the subsequent downstream effects of such increases such as raising taxes possibly politically polarizing. However, increases to federal funding of the SNS are required to sustain the SNS.

The repeated relative deprioritization of chemical agents has adversely affected the level of funding available to sustainably balance the maintenance of the SNS with the development of novel MCMs for chemical agents without an FDA-approved antidote and the improvement of existing countermeasures to address shortcomings. Project BioShield is a separate line of funding that was first established in FY2004 as a mechanism through which the government can procure MCMs prior to FDA-approval by funding private research and development efforts to address CBRN threats to national security (D.o.HS 2003, 12). Upon establishment, Project BioShield received a ten-year advanced appropriation of approximately $5.6 billion that ended in FY2013 (DHS 2003, 12). Annual appropriations began in FY2014 and consistently increased through FY2018, after which funding levels have remained stagnant until present day (Gottron and Wyatt 2023, 8). In Section 504(a) of the Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019, Congress increased the authorization for Project BioShield from $2.8 billion over 5 years (2014-2019) to $7.1 billion over 10 years (2014-2029) (US Congress 2019, 47). However, those funds have yet to be appropriated by Congress. Restoring multi-year advance appropriations for Project BioShield instead of an annual appropriation schedule can be considered, as surety of funding will contribute to stabilization and sustainment of investing in MCMs against chemical agent threats. Given the decades it often takes to take a drug from the benchtop to FDA approval, multi-year budgeting serves as the ideal focus area of improvement. Multi-year funding lines which can then translate to multi-year grant opportunities can be used to fund researchers in the development and optimization of MCMs for chemical agents.

IV. Conclusion

In order to optimize preparedness against chemical threats, it is critical to invest in improving existing MCMs by addressing current shortcomings and developing novel MCMs for potential chemical threats currently lacking an FDA-approved antidote. While chemical threats have been routinely deprioritized in yearly threat assessments, they generally cause a rapid onset of devastating consequences to exposed populations. As such, additional appropriations to the SNS and to Project BioShield via multi-year advance appropriations are recommended in conjunction with revisions of the PHEMCE annual SNS review mandate to include

mechanisms for accountability. These changes will support the research and development of MCMs against potential chemical threats in a constantly changing threat landscape and promote dynamic preparedness against established and upcoming threats.

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Aishwarya earned a M.S. in Biotechnology (concentration: Biodefense) from Johns Hopkins University and participated in a multi-year internship researching chemical warfare agents through the Oak Ridge Institute for Science and Education. This helped her gain a unique perspective on role of sustained basic science research targeted towards understanding and treating CBRN threats. She also realized the importance of technical scientific expertise at the policy-making level. Through the American Society for Biochemistry and Molecular Biology's Advocacy Training Program, she has been figuring out how to integrate her passion for science and policy. Aishwarya is currently a Ph.D. student in Biodefense at George Mason University.

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