COMMENTARY

A SECURITY TAKE ON *SAFEGUARDING CHILDREN:* *PEDIATRIC MEDICAL COUNTERMEASURE RESEARCH*

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TWO YEARS AGO I joined a group of experts across federal agencies to discuss the findings of an exercise dubbed “Dark Zephyr.” The Department of Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response (ASPR) developed this exercise to test the US government’s capacity to deal with the aftermath of a large-scale attack involving a biological weapon. This particular simulation examined what would happen during the mass distribution of *Bacillus anthracis* spores, the causative agent of the disease anthrax.

The projected outcomes, although alarming, did not surprise those who worked on issues pertaining to weapons of mass destruction (WMD). Nearly 8 million people could be exposed if a mass anthrax spore release took place in a city such as San Francisco, and almost a quarter of those exposed would be children. Many of those infected would die if left untreated. Despite a stressful situation rife with uncertainty, local, state, and federal agencies would have to provide an integrated response involving coordinated communication strategies, predictive plume modeling, forensics, intelligence collection, and distribution of medical products from the Strategic National Stockpile (SNS) through points of distribution.

Dark Zephyr deliberately focused on the distribution of medical countermeasures (MCMs), including vaccine. Protocols developed by the US Centers for Disease Control and Prevention (CDC) to treat exposure to *B. anthracis* include the use of anthrax vaccine adsorbed (AVA) for both adults and children. Accordingly, much of the Dark Zephyr analysis focused on the amount of vaccine in the SNS, the

speed with which vaccine could be delivered, and public acceptance of the MCM.

One of the issues raised during the discussion was the absence of any definitive evidence regarding AVA use with children. Although vaccine administration is included in treatment protocols for children, did we know if it was effective? Did we know if the dosing was correct? Did we know whether it would even be accepted by parents and caregivers? These are difficult questions with no easy answers—answers that we need before we can be confident that preparedness and response plans for a mass anthrax distribution event would adequately provide for the care of children. Beyond the matter of MCMs for anthrax loomed the even larger question of how to obtain the best scientific evidence for pediatric treatment in the face of WMD threats more generally, particularly those cases where no therapy yet exists.

THE BIOETHICS COMMISSION’S CHARGE

In January 2012, HHS Secretary Kathleen Sebelius charged the Presidential Commission for the Study of Bioethical Issues (the Bioethics Commission), of which at the time I was a member, to study the ethics involved in research of MCMs with children. This request came as a result of findings from the National Biodefense Science Board (NBSB) that the US government should study the safety and immunogenicity of AVA for children before an anthrax attack occurs, pending thorough ethical review.

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While the Bioethics Commission set out to draft an ethical framework for all pediatric MCM research, we spent a great deal of time on the question of AVA research with children. AVA is approved by the US Food and Drug Administration (FDA) for prophylaxis against exposure to *B. anthracis* for adults likely to be exposed to the pathogen. It has been used for decades, mostly by the military. As a US Army reservist and veteran of Operation Iraqi Freedom, I have received this vaccine. Despite many years of using AVA and collecting safety data in adults, questions remain about optimal adult dosing schedules. Moreover, there are no immunogenicity or safety data in the pediatric population. The Bioethics Commission's deliberations took into account this absence of pediatric data, juxtaposed in part against the real but uncertain threat of a bioterrorism attack and the protection of American children.

The Bioethics Commission faced the need to reconcile 2 key ethical considerations in this context: the government's duty to protect individual children from undue research risks, and its obligation to be prepared for an attack in order to protect all children to the extent possible.

THE BIOETHICS COMMISSION'S DELIBERATIONS

Research with children is ethically distinct from research with adults, especially when the research in question promises no prospect of direct benefit for the participants. The Bioethics Commission relied on established principles and practices found in the sentinel reports *The Belmont Report*¹ and *Research Involving Children*,² both produced by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974-1978). HHS and FDA codified the National Commission's recommendations for pediatric human subjects research protections in regulation at 45 C.F.R. Part 46, Subpart D, and 21 C.F.R. Part 50, Subpart D.

With these anchor points, the Bioethics Commission studied and deliberated at 4 meetings over the course of a year, releasing a report, *Safeguarding Children: Pediatric Medical Countermeasure Research*,³ on March 19, 2013. Because of the complexity of the issue and the thoughtful deliberations required to address them, the Bioethics Commission devoted more time to this topic than it had initially anticipated. Recognizing that the health and security of children is paramount, we took additional time to fully investigate all the necessary considerations to protect children both as research participants and as members of society to the greatest extent possible in the event of an attack. The deliberations proceeded through numerous avenues and iterations, which, given the gravity of the question asked, were both necessary and appropriate. In the end, the Bioethics Commission concluded that many significant steps would have to be taken—including additional

minimal risk research with adult volunteers—before prevent pediatric anthrax vaccine trials should be considered by the US government.

As the Bioethics Commission's thinking coalesced, all agreed that preevent testing posed very different ethical questions and would require different ethical considerations than testing during or immediately after an attack (postevent). Accordingly, the Bioethics Commission partitioned its recommendations along these lines.

PREEVENT PEDIATRIC MCM RESEARCH

Established doctrine and regulations regarding the ethical conduct of research involving children indicate that it should generally pose no greater than minimal risk to participants (45 C.F.R. § 46.404) unless it offers the prospect of direct benefit (45 C.F.R. § 46.405) or is likely to generate vitally important knowledge about the participants' condition (45 C.F.R. § 46.406). It is apparent that children involved in preevent research would not meet either of the latter 2 requirements: The children would not receive any direct benefit, nor would they have a condition about which the research would generate knowledge. However, this does not necessarily negate the possibility of preevent MCM research with children; it only means the research must be considered minimal risk. The risks posed by minimal risk research should be no greater than those of everyday life or a routine medical examination. In the case of AVA, such research would require prior studies in adults to identify, characterize, and understand the risks to children before proceeding to pediatric trials. The minimal risk threshold might then be achievable by studying AVA in an "age de-escalation" manner, in which studies are conducted first in young adults, and then trials are conducted in a step-down fashion with younger teenage participants and eventually with younger children if the research is found to pose no more than minimal risk.

In cases where minimal risk preevent pediatric MCM research is impossible, the Bioethics Commission determined that proposed research posing greater risk could be reviewed under 45 C.F.R. § 46.407 if it involved no more than a minor increase over minimal risk. This provision requires a national-level review, and approval would hinge on whether certain conditions were met before research would be allowed to proceed. Before approving this type of research, by regulation, the Secretary of HHS must determine that the protocol under review meets all of the following conditions: (1) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (2) the research will be conducted in accordance with sound ethical principles; and (3) adequate provisions are made for soliciting the permission of parents or guardians and the meaningful assent of children.

If a proposed research trial poses a minor increase over minimal risk, the Bioethics Commission recommended that reviewers be required to employ the rigorous ethical framework that it developed in its report. The ethical framework clarifies the circumstances in which proposed research presents a “reasonable opportunity” to address a “serious problem.” The Bioethics Commission defined “serious problem” using established risk principles, mainly threat (or likelihood) of exposure and consequences of the exposure. With this conceptual definition as a backdrop, the Bioethics Commission described the importance of a deliberative mechanism to clearly articulate these elements either to the public or to authorized representatives of the population when the information is classified. It is imperative that the information and rationale be entirely vetted before any thought is given to forgoing the protections of a vulnerable group of the population in the name of security.

In addition, the Bioethics Commission specified in the ethical framework a rigorous set of conditions necessary to determine whether the research would be conducted in accordance with “sound ethical principles,” including: ethical threshold of acceptable risk and adequate protection from harm, ethical research design, post-trial requirements to ensure ethical treatment of children and their families, community engagement, and transparency and accountability. It also requires a plan to compensate or treat individual children in cases where they suffer research-related injury. The ethical framework reiterates the importance of informed parental permission and meaningful and developmentally appropriate child assent.

POSTEVENT PEDIATRIC MCM RESEARCH

In addition to the requirements listed above, the Bioethics Commission recommended, among other things, that efforts should be undertaken now to enable and execute an appropriate research design for postevent research and to ensure widespread distribution of the MCM in the event of an attack. These measures will ensure that the US government has met its obligations to both protect the population and institute appropriate measures for the ethical conduct of research with children.

The Bioethics Commission understood that in a postevent scenario, the circumstances change and the ethical considerations are more straightforward. Because the threat is no longer theoretical, but in fact real, the preconditions required by regulation are met—for example, the prospect of direct benefit to those exposed or the potential for generalizable knowledge of a participant’s condition. Therefore, postevent research is necessary both as a matter of beneficence (ie, offering benefit to children) and of justice in fulfilling society’s obligation to secure the well-being of its most vulnerable citizens. Although the Bioethics Commission recognized that conducting studies in a postevent environment would be more technically challenging than

preevent, this loss of research fidelity was not sufficient reason to disregard ethical norms.

The Bioethics Commission acknowledged that situations might present themselves that do not neatly fit into either a pre- or postevent scenario. There is a possibility that a situation could exist where an event is “substantially certain to come about very soon and there is little to no time for deliberation or choice of action.” The Bioethics Commission defined this as an “imminent threat,” and in this context, the definition of imminence is consistent with the accepted understanding that there is an immediate and real threat to health and well-being. As such, the ethical considerations in the context of an imminent threat are considered most like those under the postevent situation in which the US government is no longer in an anticipatory mode but rather in response, and the preconditions of the prospect of direct benefit or the potential for generalizable knowledge about a participant’s condition, therefore, have been met.

CONCLUSION

The Bioethics Commission concluded that the federal government would have to take multiple steps before anthrax vaccine trials with children could be ethically considered. We made 6 recommendations that set forth the conditions under which pediatric MCM research, including anthrax vaccine trials with children, could proceed ethically in both a preevent and a postevent situation. Four of the 6 recommendations are specific to preevent pediatric MCM research, and 2 are specific to postevent pediatric MCM research.

Given my prior position in the national security community, I understand that we are challenged in considering these issues to develop policies that reflect reality, all the while knowing that the security complex can often be nuanced and sometimes ignorant in the perception of risk. As much as we who work in national security endeavor to protect the nation against unspeakable harm, this goal does not permit us to supersede other societal norms. Convenience must not supplant our society’s ethical mores. Decisions to proceed with pediatric MCM research should be cautious and deliberative and our approach balanced. This prudent and deliberative approach was captured in the Bioethics Commission’s report. I, for one, am comforted by the development of this ethical guidance as we simultaneously protect children enrolled in research studies while also doing our best to develop the knowledge needed to save children’s lives during a possible emergency.

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