Perspective Piece

Advanced Preparation Makes Research in Emergencies and Isolation Care Possible: The Case of Novel Coronavirus Disease (COVID-19)

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Abstract. The optimal time to initiate research on emergencies is before they occur. However, timely initiation of high-quality research may launch during an emergency under the right conditions. These include an appropriate context, clarity in scientific aims, preexisting resources, strong operational and research structures that are facile, and good governance. Here, Nebraskan rapid research efforts early during the 2020 coronavirus disease pandemic, while participating in the first use of U.S. federal quarantine in 50 years, are described from these aspects, as the global experience with this severe emerging infection grew apace. The experience has lessons in purpose, structure, function, and performance of research in any emergency, when facing any threat.

The University of Nebraska Medical Center and its clinical partner Nebraska Medicine (UNMC/NM) were confronted with a unique set of circumstances at the start of the U.S. experience with novel coronavirus disease (COVID-19) that highlighted core lessons regarding research in emergencies that might be applied in any location, and to any disease. Ultimately, UNMC/NM conducted a prospective, observational cohort study beginning with COVID-19-infected persons in isolation care. The rapidly traveled road to this study had many curves.

The University of Nebraska Medical Center and its clinical partner Nebraska Medicine are accustomed to responding to public health emergencies. It cared for patients with Ebola virus disease from West Africa; received persons exposed to other high consequence pathogens; established and maintained the Nebraska Biocontainment Unit; with partners Emory University, Bellevue Hospital, and the CDC, led the National Ebola Training and Education Center (NETEC); launched the National Quarantine Unit funded by the Health and Human Services (HHS) Assistant Secretary of Preparedness and Response office; and established the Global Center for Health Security to coordinate its other national and international health emergency initiatives. The biocontainment unit was established in the aftermath of outbreaks of severe acute respiratory syndrome coronavirus (SARS-CoV) and avian influenza A in the early 2000s, getting its first use in the 2014–2016 West African Ebola virus disease epidemic. The unit has critical care capabilities. The quarantine unit has airborne precaution capabilities but was designed to accommodate groups of individuals who are not ill, a need suggested by returned healthcare workers following occupational exposures in the West African epidemic. Even for an institution with experience in both timely research and management of patients with highly communicable diseases, the conditions under which coronavirus disease (COVID-19) was introduced to the United States and the pervasive challenges of patient-centered research in emergencies complicated considerations (Figure 1).
encountered in the United States. In late 2019, UNMC/NM opened the first national quarantine unit. This twenty-bed unit is designed to host larger numbers of quarantined persons than existing, smaller quarantine stations. It is colocated with a national training resource for public health emergency personnel, in close proximity to the Nebraska Biocontainment Unit, to enable more advanced care if needed. This large group of 57 persons, however, were managed by federal authorities at Camp Ashland—a Nebraska Army National Guard base outside of Omaha—with some logistics support from UNMC/NM.

By the time that the quarantined persons from Wuhan arrived, experts had already considered the possibility that SARS-CoV-2 might shed before symptoms, facilitating its ability to achieve sustained human-to-human transmission. For this reason, UNMC/NM initially sought to test asymptomatic individuals to inform their case management and how they were housed. However, a consensus regarding the advisability of testing could not be reached with authorities because of concerns regarding their personal autonomy (whether the quarantined persons understood the implications of testing and could make a choice freely) and uncertainty about what to do about isolated negative test results. Testing was not pursued. In the end, none of the quarantined evacuees from Wuhan demonstrated clinical evidence of COVID-19. The question of scope of presymptomatic shedding remained unanswered.

Toward the end of that quarantine, on 17 February, UNMC/NM received a group from a cruise ship in Japan comprised mostly of COVID-19–infected persons. The infected individuals were under federal isolation orders as opposed to quarantine; they were known to be infected. Whether simply being observed in the setting of few or no symptoms, or more ill and in need of hospital level care, they were housed at UNMC/NM. By that time, Asia had accumulated many cases, and a literature base was developing. Nonetheless, cases in the United States remained few, and availability of information and specimens from affected areas in Asia that were relevant to medical countermeasure development was limited. This prompted UNMC/NM to launch its own research initiative for the prospective assessment of patients. It did so against a backdrop of initial hesitancy because of complex issues of patient autonomy under federal orders, interagency jurisdiction challenges as different governmental actors exercised their perceived obligations for oversight, and known larger patient populations in other countries that might make local research less important.

**GOOD SCIENCE IN EMERGENCIES HELPS RISK MANAGEMENT DECISION-MAKING**

Once the decision to initiate research was made, one of the immediate questions was on what? UNMC/NM participated in the National Institute of Allergy and Infectious Diseases (NIAID) studies of drug therapy against Ebola virus disease, and this collaboration continued in support of an adaptive randomized controlled trial with the antiviral drug remdesivir. As the first institution to initiate this trial for COVID-19 patients in the United States, UNMC/NM assisted expansion of the trial to additional sites via its rapid response central Institutional Review Board (IRB) mechanism for the NETEC Special Pathogens Research Network.

Finding an effective drug, however, is not the only purpose of doing research in emergencies. Early in response efforts, a critical questions and ethics committee was formed. Pulling from a multidisciplinary base, its purpose was providing a space for leadership and others to air questions, concerns, and challenges that might represent an obstruction to effective risk management—a space to reflect amidst an otherwise operationally fast-paced environment. Fielded questions were sometimes narrow and sometimes broad. They often
highlighted uncertainty about the disease itself, which limited the ability to make evidence-based decisions. This process facilitated stakeholders coming together to start pursuing answers (Box 2). The committee also undertook a survey of research associated with the response and started to link risk management challenges with sources of information that might assist decision-making. Several needs were evident as research planning discussions ensued (Box 3). Importantly, these discussions led to a broad picture of how a platform for research might be applied, and a prospective, observational cohort study design was selected.

HAVING PREEXISTING PROTOCOLS IS VERY HELPFUL

Fortunately, the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) and the World Health Organization (WHO) had been working on a protocol for just such a prospective, observational cohort study for several years. Known as the Clinical Characterization Protocol for Severe Emerging Infections, it represents a longitudinal effort to generate and keep updated an internationally harmonized protocol for the evaluation of emerging infections.

The existence of a well-developed protocol with case report form, informed consent documents, and other supporting material had immediate advantages. From a science management perspective, the most striking aspect was that the well-documented evolution of the protocol simplified local scientific review requirements. Moreover, it was easier to edit than to initiate writing. UNMC/NM changes to documents reflected technical preferences, differences in local law or institutional requirements, or using the documents in a referral academic center rather than a resource-limited setting. Overall, the ISARIC materials saved at least several days in the process and provided important guideposts.

STRONG STRUCTURES MUST ALSO BE FACILE

UNMC/NM have several unique features in its IRB. The IRB has technical breadth, a dedicated pool of community representatives, and a process for rapid review. In addition, the university has invested in this office so that when called upon for rapid reviews, there are sufficient highly committed staff to participate in management and oversight of the process, as well as consultation with petitioning investigators. Just as importantly, the IRB has experience with reviews in emergencies and related exercises. It also has worked through how to facilitate cooperative research through its central IRB mechanism for the Special Pathogens Research Network, comprising 10 academic centers that serve as regional referral isolation care hospitals. The regulatory process reflects a general posture toward discovery in parallel with clinical care shared across its network partners. Operational efficiency such as that provided by the central IRB was impactful in ensuring the window of opportunity was not lost.

A curious, structural aspect of research preparedness that became clear while assisting other sites considering adoption of the UNMC/NM prospective, observational cohort study was the importance of routine access. UNMC/NM and other referral location personnel regularly access isolation care spaces in training and response activities, as well as participate in community coordination in the management of patients who may have an infection with a high consequence pathogen. Consequently, the primary pool of investigators...
needed at the bedside and in the laboratory are readily able to undertake practices and follow procedures within containment areas, including Institutional Biosafety Committee–appropriate laboratory spaces. Consequently, when an emergency such as the COVID-19 pandemic occurs, the work is feasible.

In each emergency, some structures preexist, some must be applied anew, and priorities must be set. For COVID-19 with a remdesivir drug trial from NIAID on site and its potential impact care generally, UNMC/NM tiered offers of enrollment to its patients, first screening for the drug trial before considering other research on a given patient.

EVERYONE HAS REQUESTS THAT MUST BE MANAGED

In just over a week from conception, in the beginnings of delivering isolation care, seven participants with COVID-19 infections were enrolled in a prospective, observational cohort study for severe emerging infections. The study rapidly accumulated both prospectively collected and residual clinical specimens. In contrast to accumulated experiences in Asia and some other affected areas, the cohort was small. Nonetheless, it captured high-quality specimens coupled with data of value to researchers and product developers in the midst of a new emerging infectious disease.

The UNMC/NM prospective observational cohort study incorporated a tissue bank, allowing the later use of study specimens. In accordance with regulatory requirements, it has a governance structure. A Priorities Steering Committee was established immediately, including some members of the investigator group and other stakeholders. A formal request process for use of data and specimens was instituted, and a request tracker quickly filled with governmental, academic, and industry requests that were as varied as they were rapid. The committee adopted a long view for use of the tissue bank, recognizing the need to balance exigent with future requests.

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FUNDING IS COMPLICATED

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challenging to fund. Research dollars tend not to align with durable, multi-threat capabilities.\(^{17}\) Such studies may be supported in part through sub-study funding, for instance, to test a particular device and assay in the laboratory on samples from cohort members. Without new funding solutions, the development of valuable cohorts may not be possible.

**SUMMARY**

The University of Nebraska Medical Center and its clinical partner Nebraska Medicine quickly established a prospective, observational cohort study for severe emerging infections during the 2020 COVID-19 emergency, while supporting national quarantine and isolation care activities and launching an NIAID randomized, controlled drug trial. This was possible thanks to preexisting resources from the international community and durable partners, as well as structures that support research review and execution with intrinsic aspects that allow flexibility. Studies in emergencies must be designed in ways mindful of the context in which they start, and yet have a long view. As in all science, aims must be clear, mechanisms for governance present, and opportunities for reflection and input encouraged. Despite challenges and sometimes a lack of external funding support, research is a worthwhile undertaking to advance understanding and seek risk management solutions.

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