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REVIEW

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Emerging infectious disease laboratory and diagnostic preparedness to accelerate vaccine development

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ABSTRACT

Rapid vaccine development in response to an outbreak of a new emerging infectious disease (EID) is a goal targeted by public health agencies worldwide. This goal becomes more complicated when there are no standardized sets of viral and immunological assays, no accepted and well-characterized samples, standards or reagents, and no approved diagnostic tests for the EID pathogen. The diagnosis of infections is of critical importance to public health, but also in vaccine development in order to track incident infections during clinical trials, to differentiate natural infection responses from those that are vaccine-related and, if called for by study design, to exclude subjects with prior exposure from vaccine efficacy trials. Here we review emerging infectious disease biological standards development, vaccine clinical assay development and trial execution with the recent experiences of MERS-CoV and Zika virus as examples. There is great need to establish, in advance, the standardized reagents, sample panels, controls, and assays to support the rapid advancement of vaccine development efforts in response to EID outbreaks.

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1. Introduction

The World Health Organization (WHO) has published a list of priority pathogens[1] as those diseases with high morbidity and mortality or with strong epidemic potential. One of the clear gaps affecting both public health efforts and vaccine development programs for any of these pathogens is a lack of standardized reagents and methods to test for evidence of current or prior infection.

The need for fast and accurate diagnostic tests of infection in an outbreak situation is obvious: identify the source or epicenter so that appropriate health-care measures can be quickly instituted. Expanding that concept to the public health scale and attaining accurate infectious disease diagnoses allows for better understanding of the course and severity of an outbreak and aids decision-making for population-level countermeasure implementation.

The clinical assays with which the immune response and pathogen presence are measured in vaccine trials become part of the basis for licensure for all vaccine products.[2] Because vaccines are tested in healthy populations through all phases of clinical development for immune response and/or pathogen presence, the methods selected to measure vaccine responses and endpoints are critical. While the identification of an immune correlate of protection for each new vaccine is highly desirable, it is not always attainable.[3]

Here we will use our recent experiences with the Middle East Respiratory Syndrome coronavirus (MERS-CoV) and Zika virus (ZIKV)[4–9] outbreaks and ensuing public health countermeasures for containment and vaccine development as examples of challenges faced during emerging infectious disease emergencies.

2. Biological reference materials and international standards

International reference materials and standards allow for a common set of reagents for a given pathogen to be available for the evaluation of the quality and consistency of clinical assays and to enable comparisons of assay data between studies. Such reference materials are established with rigorous evaluation and collaborations between multiple international laboratories and are typically assigned an international unit of measure at the completion of this process.[10] The WHO also provides guidance for the development of individual secondary standards and their calibration to accepted international standards.[11] This allows individual laboratories to maintain their own standards material that is traceable to the accepted international standard and not deplete the limited supply of the standard prematurely.

Efforts are currently underway to alleviate the international standards issue for MERS-CoV and ZIKV. Antibody and nucleic acid standards are in development for MERS-CoV, though the additional source material is being sought.[10] In 2016, the WHO initiated a collaborative study effort for the development of ZIKV nucleic acid standards[12] and, in 2017, made available a plasma sample panel through the US Food and Drug Administration (FDA) for evaluation of ZIKV immunoassays.[13] The acquisition, characterization, and standardization of relevant pathogen strains such that the strains reflect what is currently in circulation and not just a prototype strain is also of concern. For EIDs, there can be an added complication

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for sharing such material if the disease is caused by a select agent requiring enhanced biosafety measures.

Many of the priority pathogens identified by WHO cause outbreaks that are difficult to predict and may be sporadic in nature.[1] This complicates efforts to establish processes ahead of any outbreak to collect valuable acute and convalescent samples from individuals naturally infected by the respective viruses. There was, and still is, a lack of well-characterized human specimens from naturally infected MERS-CoV and ZIKV subjects that vaccine development groups could use to for assay development and, eventually, to establish a recognized set of standards that can be maintained over time.[10]

A potentially valuable source of relevant clinical samples is from ongoing epidemiological studies and clinical trials. Study designers should take care to incorporate proper language into the informed consents of participants to allow for the request of additional blood draws or sample collections and for the future use of their clinical samples for the purposes of standards and assay development.[14–16] Such studies should also ensure that well-established chain-of-custody, sample handling, and sample storage procedures are in place to maintain the quality of these valuable specimens.[17,18] A significant drawback of this approach is that often the samples may not have adequate characterization, may be of limited volume, and are proprietary to the study sponsors. It should also be taken into account that local laws or culture may be prohibitive to allowing specimens to be stored for future testing.[16,19–23] A concerted effort and willingness among researchers and companies to share available clinical specimens would be a valuable step forward in EID preparedness.[24]

Sample collection & handling are critical to the quality of the specimen and its ability to be used in assays, standards or controls.[25] Even in vaccine studies conducted in developed nations, challenges to appropriate sample collection and handling can occur. We experienced an issue with the timing of specimen intake and handling at a biorepository used for our ZIKV trials which required immediate corrective action to de-risk samples collected at the remaining study time points and prior to initiation of a second study. Ensuring proper sample storage and shipping conditions, processing and aliquotting (with attention to contamination control), training of site and clinical research organization lab personnel, a clear chain of custody from collection to final application, intermediate quality control checks, and good data management is critical for collection of high quality samples that can be used in the future.[17,26,27]

3. Vaccine clinical assays, reference reagents, international controls

In the case of EIDs, it can be difficult to predict what assays will be most useful or informative or will perhaps even provide an immune correlate of protection for a vaccine in early development. Little may be known about the basic virology or immunology of a new pathogen, though the need for developing vaccines and therapeutics is urgent.[9] Some typical methods used as vaccine clinical assays are antibody-binding ELISAs, virus neutralization or bactericidal immunoassays, IFNγ-ELISpot or related cellular immune methodology using the target antigen or antigen-derived peptide pools, and detection of the pathogen through molecular or culture assays. Vaccine clinical assays measuring humoral and cellular immune responses developed early in a program will likely evolve as clinical development progresses or as the scientific knowledge base of the pathogen and relevant immunology broadens. As improvements in technology occur over time, early vaccine assays are often re-designed and bridged to assays with higher throughput, multiplexed detection, reduction of sample volumes, and automation to support testing of large numbers of specimens for late-stage clinical trials.[28–35] Often, a variety of tests are evaluated early in the program and, based on the usefulness of the data, a down-selection occurs so that the most relevant few remain to support large Phase 3 clinical trials and licensure of the vaccine.[2,35,36]

Accepted "gold standards" of immunoassays for use at the onset of an EID vaccine program are rare. Critical reagents, standards, and controls must be monitored for consistent sourcing, batch-to-batch variability and overall quality over time. The implementation of partnerships between governmental agencies, academic researchers and industry researchers to help secure these items for the identified priority pathogens before a need should arise is of great importance.

Reagents for newly emergent infectious diseases like MERS-CoV and ZIKV were not readily available from commercial vendors at the outset of vaccine development programs. As such, individual vaccine projects, including our own, had to rely on internally developed clinical assays to understand vaccine-related immune responses and to detect prior or current infections.[4,5] Lack of standardization, however, can confound the interpretation of results from studies using different "home brew" assays across multiple laboratories such that study results cannot be directly compared in the absence of an accepted international standard or a proficiency panel of samples.[2,10]

The vast experience of our DNA vaccine consortium allowed us to develop MERS-CoV- and ZIKV-specific tests such as ELISA, virus neutralization and ELISpot early in the development and pre-clinical testing of the respective plasmid DNA vaccine constructs.[4–6,8] These assays were evaluated for consistent performance throughout pre-clinical studies and we were able to adapt their use to support our Phase 1 and Phase 1b/2a studies of GLS-5300 MERS-CoV vaccine and two Phase 1 GLS-5700 ZIKV vaccine clinical trials.[7] As these vaccines move further into clinical development, work will need to continue to transition from our pre-clinical and early stage standards to well sourced and characterized human control reagents. The concern always remains, however, that the inability to use formally characterized and internationally accepted reagents and controls in early versions of vaccine clinical assays can result in maintenance challenges or regulatory hurdles later in the vaccine assays' life cycle.[37]

4. Diagnostics for emerging infectious diseases

Diagnostic assays are often the same style tests as those used in vaccine development, like antibody binding or molecular detection. However, their intended purpose is to accurately identify the infecting pathogen to enable health-care

professionals to initiate appropriate treatments and prevent further transmission of disease. Laboratory confirmation of a diagnosis for patient treatment must have sufficient clinical sensitivity and specificity to be useful, the criteria for which may be different than analytical sensitivity and specificity criteria specified by assays for use in vaccine trials.[38–45]

Very few tests have gained Emergency Use Authorization (EUA) from the FDA. There are 2 MERS-CoV diagnostic tests, both molecular-based viral RNA detection, which received EUA in 2013 in response to the recognition of the significant potential for a future public health emergency.[46] For ZIKV, currently, 5 serological kits and 14 viral diagnostic kits have been granted EUA status.[47] For ZIKV in particular, the response to the need for diagnostics was quite rapid with all EUA approvals rolling out over approximately 19 months from February 2016 through September 2017,[46] shortly after the declaration of a public health emergency. Outside the US, the WHO's Emergency Use Assessment and Listing procedures (EUALs) recognizes the need and can grant authorization for use of diagnostic kits in emergency situations.[48] Although no MERS-CoV or ZIKV diagnostic kit, serological or viral, have been fully approved by the FDA to date, the FDA has worked collaboratively with developers to accelerate the approval process when outbreak conditions warrant.[49] A number of published studies have evaluated EUA tests independently for relevant sensitivity and specificity performance or in comparative studies[32,39,50–56] to aid in the selection of appropriate tests for the needs of epidemiological surveillance or public health diagnostics. Details outlining the relevant assay performance characteristics of each of the EUA-approved MERS-CoV and ZIKV assays can also be found on the FDA Medical Countermeasures webpage.[46,57,58]

In the instance of MERS, EUA diagnostics approvals were limited to use with select respiratory tract specimens from individuals with signs and symptoms of infection with MERS-CoV or with epidemiological risk factors (i.e., contact with probable or confirmed MERS-CoV patient or having a history of travel to locations where MERS-CoV cases occur) for the detection of MERS-CoV.[46]

For ZIKV, a number of complications in diagnostic tests such as cross-reactivity of immunological assays and short window of viremia in various bodily fluids required establishment of an algorithm to confirm ZIKV infection. This confirmatory algorithm guidance for health-care providers was based on not only clinical symptoms, risk factors, and diagnostic test results,[59,60] but also specifically for the use and interpretation of EUA diagnostic ZIKV IgM tests to indicate recent exposure with or without accompanying molecular ZIKV test results.[59] The types of specimens and timing of collection of specimens that would provide the most reliable results was also a consideration in the ZIKV diagnosis algorithm.

5. Future preparedness for EIDs

The Coalition for Epidemic Preparedness Innovations (CEPI) and others are working to ensure that rapid response mechanisms are in place to address emerging infectious diseases.[24,61,62] The CEPI coalition was launched in 2017 as an innovative concept to establish global partnerships between public, private, philanthropic and civic organizations with the goal of accelerating the development of vaccines against emerging infectious diseases and strengthening vaccine access capabilities before an outbreak situation is encountered. Funding to support development teams building the infrastructure necessary for rapid vaccine design, manufacture, and clinical assessment is being provided to help ensure that we are prepared for EID outbreaks that may occur.[62]

EID public health and countermeasure programs have unique challenges for diagnostic and vaccine clinical assay development purposes.[2,39,41,63–71] There may be an incomplete understanding of the biology or epidemiology of a new pathogen, which can delay or confound the selection of a relevant vaccine target and the subsequent assay development to be used to evaluate the candidates. The field may suffer from a lack of available reagent sources or with inconsistency in quantity and quality of those available, especially early in the discovery and development process. The difficulty in obtaining or developing relevant human sample panels, reference materials and/or international standards for the evaluation of test methods add to the challenges to support assay performance from early vaccine development through licensure.[10]

Although the speed at which the EID diagnostic or vaccine development field needs to move will be dependent upon the urgency of the pathogen outbreak and its impact on human life, scientific and quality principles must still apply when developing vaccine or diagnostic assays. Biological assay standardization is critical.[2,10,17,71,72] At a minimum, the development of relevant biological assays with adequate sensitivity and specificity for the application should use biostatistics to establish and verify assay performance and to maintain the ability to produce stable and reproducible results over time to support diagnostic or vaccine program needs. The criteria for acceptability of any given test system will be dependent upon the nature of the pathogen, our understanding of the immunology to fight the pathogen (both of which may be poorly understood in an EID situation) and the assay platform. If assay performance consistency and quality are not demonstrated, the validity of clinical study results may be questioned. In the execution of vaccine clinical trials, assay methodology must be accurate, specific and robust with high-quality procedures in place for sample collection, processing, and storage to ensure success.[25,26,36,37] The translatability of assay methodology is also important if the acceleration of vaccine development is dependent upon the use of animal challenge studies to establish efficacy or to help define a correlate of protection for an EID pathogen.

Efforts to prepare reagents, collect well-characterized samples, develop research materials, and international standards in advance for EIDs for whom alerts have already been raised, such as the WHO priority pathogens, through collaborative partnerships with governmental and philanthropic agencies along with academic and industry-based researchers will make us better suited to respond with speed to an outbreak.[24,61,69,73] Assay standardization for these or any other newly emergent infectious disease will be challenging and take time to develop, collect and characterize quality

reagents, to achieve sufficient sources samples for the establishment of serological or molecular standards.[10] The commitment of researchers and companies invested in the research, diagnosis, treatment, and prevention of EIDs to participate and contribute to organized efforts to create and validate internationally recognized standardized reagents, assays and controls for priority pathogens in advance of an emergency is imperative and the time to start building this framework is now.

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