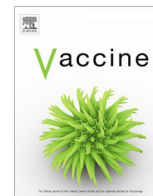




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Conference report

Summit proceedings: Biomedical countermeasure development for emerging vector-borne viral diseases

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ABSTRACT

Emerging and re-emerging infectious diseases are an expanding global threat to public health, security, and economies. Increasing populations, urbanization, deforestation, climate change, anti-vaccination movements, war, and international travel are some of the contributing factors to this trend. The recent Ebola, MERS-CoV, and Zika outbreaks demonstrated we are insufficiently prepared to respond with proven safe and effective countermeasures (i.e., vaccines and therapeutics). The State University of New York Upstate Medical University and the Trudeau Institute convened a summit of key opinion and thought leaders in the life sciences and biomedical research and development enterprises to explore global bio-preparedness challenges, take an inventory of existing capabilities and capacities related to preparation and response, assess current “gaps,” and prospect what could be done to improve our position. Herein we describe the summit proceedings, “Translational Immunology Supporting Biomedical Countermeasure Development for Emerging Vector-borne Viral Diseases,” held October 2–3, 2018, at the Trudeau Institute in Saranac Lake, NY.

1. Introduction

The Trudeau Institute (Saranac Lake, NY), in partnership with the State University of New York Upstate Medical University (Syracuse, NY), hosted a summit entitled, “Translational Immunology Supporting Biomedical Countermeasure Development for Emerging Vector-Borne Viral Diseases.” The attendees included basic scientists, physician-scientists, science support professionals and organizations and institutions with experience and expertise in identifying and working to solve major global health problems. The mission was to define today’s most pressing global health problems, identify critical obstacles which challenge the develop-

ment of solutions to these problems, and prospect how both may be overcome. Summit sessions focused on disease preparedness and vaccine development. Summit organizers desired to catalyze the formation and sustainment of productive and strategic interdisciplinary partnerships and collaborative research networks with a focus on the rapid development of countermeasures against our most pressing global health threats. Three keynote speakers representing the International Vaccine Institute (IVI), Coalition for Epidemic Preparedness Innovations (CEPI), and the U.S. National Institutes of Health (NIH) framed four concept areas which were then discussed during two individual sessions per topic; each session was defined by a specific topic and led by a pre-selected session leader. The overall organization is presented in **Box 1**.

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Box 1 Overall organization. Concept 1. What is the next emerging disease (Disease X)?

Keynote 1- How do we identify and prepare for Disease X?

- Discussion 1- How can the global biosurveillance enterprise and infrastructure be improved to better support bio-preparedness and response?
- Discussion 2- How can the global biosurveillance enterprise and infrastructure be improved to better support developing a universal flu vaccine and assessing needs of neglected populations (pregnant women, infants, etc.)?

Concept 2- Obstacles and opportunities in pre-clinical development.

Keynote 2- Prospecting future investments in animal models.

- Discussion 3- Animal models to keep and those to discard. What models have delivered and which ones have continued to deceive?
- Discussion 4- Innovative pre-clinical models and how they can support countermeasure development.

Concept 3. Moving faster to the clinic.

Keynote 3. What are the prospects for expanding global biomanufacturing and executing clinical trials?

- Discussion 5- What are the obstacles in the critical path and gaps to advancing to first in human and clinical endpoint studies?
- Discussion 6- Where are contract research organizations being optimally and sub-optimally utilized to support countermeasure development? Opportunities for improvement?

Concept 4. Demonstrating clinical benefit.

- Discussion 7- Prospecting non-traditional paths to demonstrating safety and clinical benefit of countermeasures.

2. Summit day 1

2.1. Concept 1- disease x

The first concept discussed was, “How do we identify and prepare for Disease X,” referring to the next major infectious disease epidemic or pandemic. Dr. Melanie Saville, Director of Vaccine Development from CEPI, introduced the concept by discussing possible Disease X pathogens stressing they may be currently known or unknown. This may include known threats such as Ebola, known viruses with unrecognized impacts such as Zika, and unknown threats not previously identified. Current global trends indicate that a new disease emerges every four months, and more likely than not, Disease X will emerge as zoonotic in origin, as nearly 60% of all pandemics fit that model. The need to identify a burgeoning outbreak and initiate development of countermeasures was stressed. Citing a key example from the 1918 flu pandemic, which was modeled by the Vaccine Modeling Initiative and presented recently by the Gates Foundation [1], were such a pandemic to occur today, all major cities in the world would be impacted, with 13 million dead within 60 days. A more recent example was coordination of the global response to the 2014–2016 West Africa

Ebola pandemic and the challenges with fielding and testing therapeutic and vaccine candidates [2]. A review of the Ebola response produced four key recommendations: (1) strengthen human-animal surveillance systems as the first line of defense; (2) reinforce global coordination and capabilities; (3) accelerate product development, and; (4) provide economic incentives to help.

The path to prevent a global health disaster from Disease X is global preparation that draws existing public health organizations together in a coordinated, vigorous and sustained effort that delivers a safe and effective vaccine when and where it is needed. As such, an important CEPI goal is to address both preparedness and rapid response to “Disease X” by leveraging pre-developed vaccine platforms such as injectable formulations of DNA, self-replicating RNA, recombinant proteins and viral vectors. It was recognized, however, that regulators license vaccines, not platforms, so even the use of well-established platforms for rapid vaccine development for an emerging virus may not allow for rapid regulatory approval and regulatory agencies vary globally. However, the use of pre-developed platforms could expedite the path from pre-clinical research to clinical development.

2.2. Concept introduction take home points

- We are currently too slow to comprehensively respond to emerging and re-emerging outbreaks
- Biosurveillance in high risk areas needs to be bolstered with deployment of sustainable diagnostic platforms and data-sharing capabilities
- Effective collaboration is key to successful biopreparedness and response
- Shared understanding of the situation’s gravity and effective communication of the same among stakeholders is essential
- Preparedness can be improved in many areas to include: standardizing animal models; leveraging vaccine construct platforms; growing clinical trials capabilities in high risk areas; leveraging and expanding global biomanufacturing capabilities; developing and deploying analytic assays; and streamlining regulatory pathways.
- Note added after review: The concepts discussed herein for Disease X are not limited to vector borne diseases. We deliberately chose not to include human engineered bioterrorism agents not encountered in nature, as we felt that adequate consideration would include a separate, full discussion on intelligence gathering, countermeasures, mitigation and bio-preparedness, which would be beyond the scope of the meeting agenda.

2.2.1. Session 1

The Keynote address served as an introduction to two ensuing discussion sessions. The first, “How can the global biosurveillance enterprise and infrastructure be improved to better support bio-preparedness and response”, was led by COL Matt Hepburn, from The U.S. Department of Defense, Defense Advanced Research Projects Agency (DARPA).

Session take home points

- When assessing how well the global health community currently is achieving effective biosurveillance the glass appears both half empty and half full. Modern technology (Next Generation Sequencing, NGS) has been widely implemented in the diagnosis and tracking of infectious diseases. However, there is room for improvement-leveraging the full potential of this technology has been hindered by several factors: groups working in isolation (i.e., not sharing data in a timely manner); limited access to samples from the countries most affected by an outbreak; failure to capture and annotate critical information on the time and precise location of sample collection.

- A suggestion for improving the global biosurveillance enterprise is to transition from monitoring the advance of specific outbreaks over time (vertical surveillance) to horizontal surveillance (quantifying the presence of diverse pathogens across the population over time).
- Another suggestion is to create standard criteria for assessing global viral threats—tropism, replication, structure, genotype, evolution, immune evasion, pathogenesis, animal models, and correlates of protection. However, this may be difficult for viruses that can utilize a range of hosts, vectors, etc.
- To achieve the ultimate goal of fully implemented global health biosurveillance we should be proactive instead of reactive.
- It is imperative to solve the problem of sustainable funding. A general consensus of the group on this topic was that to produce a blueprint for sustainable funding of continuous horizontal global biosurveillance, future discussions of biopreparedness need to include experts in finance, ethics, and international politics in addition to biomedical scientists, clinicians, and product developers.

2.2.2. Session 2

The second discussion session focused on a single global infectious disease threat—influenza. Dr. Bruce Innis (Program for Appropriate Technology in Health, PATH) led the discussion on, “How can the global biosurveillance enterprise and infrastructure be improved to better support developing a universal influenza vaccine and assessing needs of special populations (i.e., pregnant women, elderly, infants, etc.)?”

Session take home points

- Influenza affects different populations differently. The group asked the question, “Is there a more effective way to quantify frailty that alerts us to whom will need close monitoring during flu season?”
- Vaccines against influenza are beneficial because they modify infection outcomes in addition to preventing disease.
- Clinical trials of universal influenza vaccine candidates should implement a validated severity score for children and adults to capture the full value of the intervention. Can metrics that provide a severity score be developed and validated?
- If we can sustain multiyear clinical trials, then many important questions related to the natural history of influenza infection in a population can be addressed. For example, what is the relative efficacy in individuals with pre-existing immunity (natural or through seasonal vaccination) versus naïve children? What is the impact of co-infection with other pathogens during an outbreak of influenza? Is it possible to achieve sustained protection by exposure to multiple strains over years? These important objectives face the stiff reality that important endpoints beyond those strictly required for licensure are difficult to incorporate into already expensive and logistically challenging trials.
- Establishing field sites in low and middle-income countries for longitudinal surveillance of respiratory diseases would build globally-beneficial disease surveillance and vaccine evaluation capacity.

2.3. Concept 2- obstacles and opportunities in pre-clinical development

This concept was introduced by Dr. M. Cristina Cassetti, of the NIH. She highlighted the recent outbreaks of Ebola and Zika as experiences to help to identify areas for improvement including: surveillance on a global scale; early detection transparency and improved communication; building infrastructure capacity; better coordination of basic and clinical research; making platforms and

technologies nimble and adaptive, and; finding stable sources of funding.

Dr. Cassetti outlined that the overall approach to achieve success in preparedness will be based on the strategic, logistic, financial, and scientific. The single most important strategic component is to enhance collaborations with global partners. Partnerships must exist prior to the outbreak- with mutual trust. The NIH now is a collaborating center with WHO and CEPI, and the U.S. federal government participates in the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE). It is also important to establish relationships with local Ministries of Health. Exemplars of advancements include: (1) Logistically, an Emergency Outbreak Standard Operating Procedure (SOP) has been developed; (2) Financially, mechanisms such as the Urgent Parent Funding Opportunity Announcements (FOA) (released in Fall 2018) have been established allowing supplements to existing grants to be issued and streamlined Broad Agency Announcement (BAA) contract processes can also be utilized; and (3) Scientifically, new vaccine platform technologies can be leveraged.

Specific to animal models, the need to develop new animal models for different uses (not a one-size-fits all) was discussed. Developing highly characterized pathogen strains, assays and models to generate data that could be used to support non-traditional regulatory approval pathways was discussed.

NIH is currently developing an integrated plan to respond to emerging threats. This plan will be based on a prototype approach, where all the viral families implicated in human disease and where new viruses are most likely to emerge from (e.g., zoonotic, RNA viruses, etc.) will be evaluated to:

- (1) identify representative pathogen prototypes from each family;
- (2) systematically support/conduct research to fill knowledge gaps needed to support countermeasure development against these prototypes (e.g., mechanisms of pathogenesis and protective immunity and suitable animal models);
- (3) develop candidate vaccines/therapeutics toward evaluation in animal models and Phase 1 testing; and
- (4) build an integrated network of clinical sites around the world where the most promising countermeasures could be rapidly tested in the field for safety and efficacy and the infections can be studied in its natural setting in both humans and their vectors (natural history studies).

Additional NIAID efforts to improve biopreparedness include: (1) Developing relevant animal models that recapitulate human diseases and enable study of human pathophysiology; (2) Continuing to develop *ex vivo* models such as the brain organoid; and (3) Continue to focus on critical gaps in pathogen identification/characterization and pathogenesis [3–6]. The point was reiterated that we need to strengthen international clinical trials capacities, attempt to better align regulatory agency review requirements, and to develop more flexible funding mechanisms.

2.3.1. Session 3

The first discussion session under this concept was, “Animal Models- Models To Keep And Those To Discard: What Models Have Delivered And Which Ones Continue To Deceive,” and was led by Dr. Alan Barrett from The University of Texas Medical Branch, Galveston.

Session take home points

- Translating discovery science to preclinical development in animal models is not straightforward as the animal model should ideally recapitulate human disease. The overall value of an animal model for the evaluation of drug and vaccine candidates

requires high quality, well characterized and, preferably, standardized and validated assays and reagents and challenge materials.

- There is a spectrum of similarity between animal and human immune systems and responses to infection. These differences must be taken into account when interpreting pre-clinical data and making programmatic decisions based on the same.
- Animal models have been informative in dose selection for human studies. However, there remains variance across models and responses may over- or under-estimate what can be expected in humans (example – non-human primate responses to Ebola vaccine candidates over-estimated the human response).
- Inferring what a protective immune response in a human based on the natural infection of a pathogen-free animal can be precarious; this can be especially true when exploring correlates of protection. One may pay particular attention to differences in how a pathogen is delivered in nature (i.e., mosquito, superficial dermis, salivary proteins) and how this may or may not translate depending on how we deliver in the context of vaccination (i.e., needle, intramuscular or subcutaneous, no salivary proteins). Note added after review: Back correlations between efficacious vaccines and mechanisms of protection should be carried out to derive correlates of protection. Alternative approaches using *in vitro* organoids and *ex vivo* studies should be used to supplement live animal models, although their role in supporting product development is uncertain.
- Several other parameters of animal models can be poorly reflective of the human infection and disease experience. For example, the time course of infection in animal models can be remarkably different from humans. Further, lethal challenge models (e.g., Nipah) do not provide endpoints suitable for translation to clinical trials.
- Model relevance was also discussed in the context of a Zika pregnancy model in immunocompetent mice, in which the infected dams did not get viremia and there was no detectable vertical transmission of virus, yet there was virtually 100% fetal demise. Monoclonal antibody blocking studies indicated that, despite the absence of productive infection, the pathology was apparently caused by virus, raising the possibility of fetal demise due to specific placental pathology [7].
- There would be great value in developing high quality, standardized animal models and challenge strains of particular pathogens that are broadly accepted. Following Good Laboratory Practices within high bio-containment required for handling some pathogens is difficult and could impact countermeasure development efforts in these areas. Note added after review: Emphasis should be placed on working with bio-containment labs to get as close to GLP compliance as possible.
- Once a candidate vaccine or drug has entered into clinical testing or has been proven safe and effective it would be valuable to go back and assess how pre-clinical animal models supported or did not support informed programmatic decision making.

2.3.2. Session 4

The second discussion session under the concept of pre-clinical development was led by Dr. Kent Kester, Sanofi Pasteur, on the topic of, “Innovative pre-clinical models and how they can support countermeasure development.”

Session take home points

- *Ex vivo* models have the potential to change the countermeasure development paradigm and support moving investigational products into clinical trials faster and produce more informative and relevant data (e.g., antigen concentration or overall formulation selection).

- The partnering of *ex vivo* immunologic models with the development of experimental human infection/challenge models/tools could also be a particularly important area to explore, especially if clear surrogates or correlates of protection can be identified.
- How *ex vivo* models are used to support regulated activities remains unknown and requires considerable exploration. Countermeasure developers and Sponsors will need to engage regulatory authorities to explore if *ex vivo* human immune models can appropriately substitute for animal studies and if so, what level of evidence for this will be acceptable?
- *Ex vivo* human organ or system models may be of value especially in the study of diseases with specific characteristics which may make them difficult to study in the context of natural infection (i.e., long incubation periods, periodic occurrence, etc.).
- Vaccines proven to be safe and efficacious/effective provide an excellent opportunity to explore potential mechanisms of action and correlates or surrogates of protection for these countermeasures with applications to other related or similar pathogens. There is also the potential to explore if these physiologic and immunologic situations can be reproduced in an *ex vivo* system and subsequently applied to new explorations. Note added after review: Inversely, the ability of the *ex vivo* system to predict safety/reactogenicity issues is important.

3. Summit day 2

3.1. Concept 3- moving faster to the clinic

This topic was introduced in a Keynote presentation by Jerome Kim, Director General of the International Vaccine Institute, who discussed, “What are the prospects for expanding global biomanufacturing and executing clinical trials.” Dr. Kim presented a comprehensive overview of hurdles involved in delivery of successful global health vaccines to sites of outbreak, including: (1) the innovation gap in the discovery/pre-clinical phase; (2) the translation gap prior to clinical development; and (3) the implementation gap, affecting policy and uptake. He presented the example of rotavirus, to illustrate the impediments to dissemination of a vaccine subsequent to development, including access and cost. He also talked about how to fund “poverty-associated” infectious diseases with little market incentive for development, and proposed a combination of pharma, philanthropy, and government to develop public/private partnerships for vaccine development funding.

Session take home points

- Current funding models need to transition from epidemic-response funding to sustainable funding models which incentivize countermeasure developers.
- Anticipated expenditures on development of countermeasures for neglected diseases are not matched by the larger value proposition. De-risking the development proposition with newer tools (*ex vivo*, human challenge, adaptable design) which lower cost and time to market may help but a comprehensive analysis of global finance and vaccine market-share needs to be created and maintained.
- Countermeasure development continues to be plagued by inadequate innovation in the pre-discovery space, poor translation to the clinic, and sloppy implementation of bioproduction and distribution. In the commercial sector, innovation and creating operational efficiency are incentivized; how do we capture these elements in the global vaccine development value chain?
- The global community needs to understand how to leverage the increased capacity in biomanufacturing which is being developed in emerging markets while ensuring reproducible safety and quality.

- Note added after review: public incentives and options for the biomanufacturer may help in cases where the private market has failed. Platform technology development may aid development.

3.1.1. Session 5

The next discussion, led by John Mascola, Vaccine Research Center, NIAID, built upon the issues introduced by Dr. Kim's Keynote presentation, and addressed, "What are the critical path obstacles and gaps to advancing to first in human and clinical endpoint studies?" The discussion was organized into four topics: (1) scientific gaps; (2) limitations in Good Manufacturing Practices (GMP) capabilities and capacities; (3) regulatory issues; and (4) limitations in clinical trials infrastructure. The group concluded that the major limitation to rapid advancement of vaccines was the inability to plan and execute a full product development plan from start to finish, including the necessary end to end funding.

Session take home points

- There are diverse stakeholders to the vaccine development pipeline, including government funding, industry research and development, and public-private partnerships. CEPI can take products from late preclinical stage through Phase II development, but commercial phase vaccine development is generally funded by the private sector. Overall, there is a need for additional committed resources and organizational structure to link academic, government, philanthropy and the private sector, to better foster both the early and final commercial development of unmet vaccine needs.
- Platform vaccine technologies can be leveraged to accelerate vaccine development by addressing regulatory and manufacturing issues in advance.
- Sources of long-term funding of vaccine development are from country government sources and philanthropy- for example, U. S. NIH funding, the Bill and Melinda Gates Foundation, and the Wellcome Trust. CEPI funding is a new option, which can support early stage clinical development. A key goal is to leverage existing funding sources to attain additional investment through less traditional sources – impact investing and related approaches.
- Technical improvements in biomarkers, clinical immunoassays, and GMP manufacturing (cell lines, vectors, platforms) can lower the barriers to commercial vaccine development and distribution. Close and early collaboration with regulatory bodies can help address regulatory bottlenecks. A key remaining gap relates to sustaining the advanced clinical trial infrastructure needed to perform pivotal efficacy studies.

3.1.2. Session 6

This session was led by James F. Cummings, ICON Government and Public Health Solutions, "Where are contract research organizations (CROs) being optimally and sub-optimally utilized to support countermeasure development and opportunities for improvement?"

CROs can cover a broad range of clinical trial activities, including trial design and management, enhanced recruitment, collection and processing of clinical samples, data collection, management and analysis, and development of documentation for registration. Dr. Cummings provided numerous examples of how CROs can offer resources to supplement development programs, including flexible staffing, support for clinical trials, medical and technical documentation, intellectual property issues, filings for registration, and global reach. Flexible staffing can contribute to productivity and help an organization manage risk. Functional service provision (FSP) staffing and clinical operations span from preclinical studies to fil-

ing for market approval, and some CROs can offer these complete packages.

CROs can also be useful when issues arise in international settings, such as unexpected political and regulatory issues, corruption, and other cultural issues. CROs with well-established international partners can act as a site maintenance organization, where the CRO contracts with a network of individual providers in the host nation under the umbrella of the CRO.

Session take home points

- CROs can participate in a broad spectrum of R&D activities that enhance and accelerate vaccine development. They have created standardized case definitions, data capture platforms, reporting systems, data transmission, and regulatory filings.
- CROs can offer manufacturing perspective, including global database of available manufacturing capacity based on platform experience, terms to engage, availability, and monitoring and managing ownership.
- CROs have regulatory expertise which can fill gaps in knowledge, bandwidth and experience to effectively approach regulatory agencies, such as the European Medicines Agency in Europe (EMA) and the US Food and Drug Administration (US FDA).
- CROs can help when dealing with international sites, based on past experience. Experienced CROs develop large but simple studies appropriate to austere environments. They know how to dispense with complexities and assess what *needs* to be done in the context of what *can* be done.

3.2. Concept 4- demonstrating clinical benefit

3.2.1. Session 7

This session on, "Prospecting non-traditional paths to demonstrating safety and clinical benefit of countermeasures," was led by Tom Monath, Crozet BioPharma. Key points that were covered included: (1) the effect of antigen drift in surveillance; (2) innovations in safety assessments; (3) implementation of the animal rule; (4) use of immune biomarkers to evaluate clinical efficacy; (5) the ethical challenges of human challenge models; (6) licensure standards; and (7) wildlife vaccination.

Session take home points

- Antigen drift leads to a multitude of issues that impact the assessment of the clinical benefit of a vaccine or an antibody therapy, including: (1) defining protective epitopes across many clinical isolates; (2) determining how to establish firm evidence of clinical relevance; (3) evaluating cross protection in animals and by use of monoclonal antibodies that mediate neutralization *in vitro*; and (4) being cognizant of the potential confounding effects on *in vitro* neutralization used to calibrate vaccine dosing. Japanese encephalitis vaccines are an example of this issue.
- The group felt there was little evidence for an important role of toxicology studies in modifying the development plan, however negative toxicology studies may support advancing candidates. Newer methods of assessing safety might include replacing traditional toxicology studies with innovative technologies such as "organs on a chip," and imaging data rather than biodistribution.
- The animal rule is currently reserved for situations where efficacy is difficult or unlikely or there is a time sensitive window to prove in human phase 2b. To improve the effectiveness of the animal rule on a global scale, it was suggested that the U. S. will be the leader for "animal rule" while other regulators will await U.S. approval. It was suggested that consideration be given for a hybrid model—how and what relevant animal data can be linked to or supplement human data.

- The use of immune biomarkers to evaluate clinical efficacy is considered an important time-saving step to demonstrate clinical benefit. This concept implies there is a functional attribute to an immune/protective response. Using immune markers to support an Accelerated Approval pathway is desirable, however there are many unanswered questions about the mechanism of protection for some vaccines. Neutralizing antibodies as correlate for many viruses have been shown to be unreliable in some cases (examples–Ebola and dengue). It may be important to study survivor immune responses.
- There is a potential role for biomarkers to identify adverse events- for example, biomarkers could present an opportunity to predict reactogenicity to adjuvants.
- Passive immunization can be a valuable tool for establishing the role of antibody in protection and in determining seroprotective levels. For example, passive transfer in an arenavirus model was used to establish that both neutralizing and non-neutralizing antibodies can be protective [8].
- Ethical challenges complicate placebo controlled testing of vaccines against life threatening infections as well as use of human challenge models. For example, use of randomized control trial (RCT) in the Ebola outbreak was highly controversial. Innovative approaches such as the stepped wedge method [9] and delayed ring vaccination [10] were taken to control the vaccine trials, and efficacy was successfully demonstrated.
- Incorporating human challenge models into vaccine development for Disease X with high mortality can be done given: availability of a partially attenuated vaccine virus or pseudotyped attenuated virus for challenge; operation under the consideration of “do no harm;” and, in specific instances studying cross protection with an antigenically- related virus strategy in an emergency (example – use of approved Japanese encephalitis vaccine against the West Nile [11–13] or a chikungunya vaccine against o’nyong nyong) [14].
- Licensure standards need to be established in order to accelerate approval of vaccines. Adopting the standard of substantial effectiveness and evidence (reasonable likelihood) of clinical benefit can be valuable. The FDA has shown willingness to grant licensure for pandemic influenza manufactured in a similar mechanism to the seasonal flu vaccines. Note added after review: However, manufacturing and facility requirements pose challenges associated with validating new processes and facilities.
- Vaccination of animals responsible for transmission of agents to humans can be a very effective tool to combat the spread of a pandemic, and therefore it is important to understand the natural history of the disease. Some examples were given where accessible animals play a role in amplification and could be vaccinated to interrupt a human outbreak (example – Venezuelan equine encephalitis, Rift Valley fever, Nipah virus disease). Importantly, veterinary vaccines are faster and easier to develop, and the USDA grants a conditional approval pathway. Despite the success of this approach for control of rabies, wildlife vaccination remains virtually unexplored.
- We have many opportunities to learn from our experience. It is important to assess effectiveness and evidence of vaccine failures. There should be more efforts to make use of studying protection against subclinical or mild infections. Finding clues to correlates of protection from such cases can be used to focus development resources more effectively. Can we use Jennerian (cross reactive) vaccines in the event of an emergency (e.g., chikungunya vaccine vs. O’nyong’nyong or Japanese encephalitis vaccine vs. West Nile)?
- Note added after review: The Animal Rule is reserved for drugs and vaccines in which traditional and accelerated approval pathways are not possible, and is not directly related to a

time-sensitive window to prove efficacy in phase 2b trials. Also preclinical toxicology studies may be useful when negative toxicology findings have affected the decision to pursue product development.

BOX 2 Overarching recommendations.

- Strengthen the breadth and depth of human-animal disease surveillance; have entomologists and veterinarians engage with physicians and scientists studying human diseases.
- Reinforce, standardize, and incentivize global coordination for real-time and accurate data sharing.
- Expand global clinical trial capacity, especially in areas of emerging or re-emerging infectious disease.
- Improve pre-clinical animal models striving to accurately recapitulate natural pathogen delivery and human infection response and pathologic outcome.
- Strategically invest in exploring *ex vivo* models of disease, especially for assessing correlates/surrogates of protection of countermeasures proven to be safe and effective in humans.
- Future discussions of biopreparedness need to include experts in finance, ethics, and international politics, in addition to biomedical scientists, clinicians, and product developers.
- Standardize regulatory requirements internationally; think innovatively about licensure requirements for pathogens where traditional clinical end-point studies may not be possible.
- Develop funding strategies which provide end-to-end, secure funding scenarios for development efforts, incentivize investment by reducing risk and rewarding efficiencies and deliverables.
- Continue to explore opportunities for use of experimental human infection models when the bioethical and safety parameters meet external and objective criteria.
- Explore the network of CROs and the breadth of services and global reach they can provide as part of a larger and strategic out-sourcing strategy, especially early in development when risk is high.
- Seek new approaches to outbreak cessation such as vaccination of animals for zoonotic diseases and using licensed vaccines with potential for cross-protection.
- Enhance and pursue the prototype-pathogen and the priority-pathogen approach; use of pre-developed vaccine platforms to speed up development.
- Note added after review: Define an overall governance and leadership structure that can implement a coherent sustained strategy in developing countermeasures against potential emerging infectious diseases across national boundaries, with the necessary invested authority and resources.
- Note added after review: Leverage new tools of communication, such as social media to address epidemic surveillance and response; Determine ways of building trust in the affected population during outbreaks; Development of regulatory innovations, such as pre-epidemic regulatory convergence to expedite regulatory requirements during the epidemic.

3.3. Closing group exercise

The Summit ended with a group “war game” exercise, where the participants were divided into two teams and were tasked with developing countermeasures in environments with variable risk tolerance, financing and timelines. The exercise, although somewhat simplistic in its design, was powerful in its demonstration that there is considerable room for re-thinking assessment of risk and finding opportunities for efficiencies (example – development speed) when it comes to countermeasure development.

Important take-home points are summarized in **Box 2**. There was considerable enthusiasm at the close of the summit for additional and similar interactions in the future, with the important addition of defined and tangible deliverables. It was also agreed the pool of experts needed to be broadened to include finance, ethics, and international politics. Such a meeting is actively being planned.

4. Disclaimer

The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the official views of their respective organizations.

Declaration of Competing Interest

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