World Health Organization

Meeting summary

What are the key next scientific steps?

Philip Krause, MD
Advisor to WHO

A scientific framework for epidemic and pandemic research preparedness
Scientific opportunities to achieve fast and equitable access to high-quality and trusted vaccines for future pandemics.

9 Jan 2024

R&DBlueprint
Powering research to prevent epidemics

Summary

This is the first of a series of consultations, addressing epidemic and pandemic research preparedeness regardless of perceived pandemic potential. Later consultations will address priority pathogens, pathogen X, and generation of randomized evidence.

Although new pathogens continue to be discovered, virus families are generally known. Around 150 viruses from 26 families have some pandemic potential. Focusing on prototype pathogens will provide generalizable knowledge about families. Pandemic preparedness is needed for optimal pandemic response.

Pathogen family approach will require increased breadth of planning, while maintaining focus on key pathogens which will be prototypes for their family. This will require detailed knowledge of viral characteristics, preclinical & clinical development of prototype vaccines 7 therapeutics, and manufacturing & storage of stockpiles. Collaboration is essential.

Importance of Quality, Equity, Trust, Speed and Cost in pandemic response, with **global collaboration** as a key goal.

Summary (pathogen discovery & threat detection)

Pathogen capture based sequencing can speed pathogen identification to <8 hours from sample receipt. Numerous examples of use of these techniques to detect pathogens in mini-outbreaks which are also being deployed around the world.

“Smart surveillance” focuses on spillover risk. Look at wildlife, community (e.g., serological assays), and clinic with assay development & characterization behind the scenes. Potential risks can be further defined with additional research (e.g., receptor binding).

Importance of increasing availability of non-specific surveillance approaches around the globe, with appropriate community & host country engagement. This requires long term investment in research and embedding new technology in key settings, including “hot spots”, and willingness to rapidly deploy research assays. Coordination of animal & human research, along with capacity building and retention, is important. Key samples: animals, wastewater, humans. Higher yield expected from surveillance in humans at animal-human interface. Research on monoclonal antibodies is at nexus of key immunological goals, also high throughput serological analysis using properly folded proteins, including cellular responses.

Summary (basic research, immunology)

Structure based vaccine design enhanced by advances in Cryo-EM. High like DARPin can be used to image small proteins. EMPEM allows visualization of immunodominant epitopes in polyclonal immune responses. AI/ML approaches to study microenvironment around amino acids to improve antigen design.

How to translate genetic information into “functional viromics” to understand zoonotics and cross-species potential? Tropism influences pathogenicity, requires understanding of receptor, RBD interaction. Can be studied via coprecipitation with goal of comparative analysis to predict receptor binding of mutants. Host innate immune interferences also critically important for pathogenicity.

MAb discovery has progressed from hybridoma, through phage dislplay, B cell reverse vaccinology to machine learning. MAbs can be used to discover & stabilize antigens that induce similar responses (early examples: HIV, RSV). Also can be used for assay development, define CoP.

Summary (basic research, animal models)

Animal model group has helped to develop and standardize aniamal models since 2/20, enhancing availability, enabling preclinical development of COVID-19 vaccines and study of enhanced disease, assessment of VOC transmission and secondary hosts. Data & reagent standardization with emphasis on sharing. Importance of WHO collaboration, cellular immunity, reagent sharing (biobank?), development of humanized pathogen-specific animal models emphasized. Deletion of murine interferon, addition of human interferon and viral receptor can improve organ-specific models.

Tools to improve animal models, eg.CRISPR/CAS-9 which allows precise targeting, but also include random integration, gene targeting in embryonic stem (ES) cells via homologous recombination which permit larger insertions, viral targeting. Confer infectivity/susceptibility, humanized antigen presentation (e.g., human MHCs), humanized immune ystem (e.g., cytokines & immune factors), humanized antibodies (including chimeric Abs). Pre-pandemic work could include HLA expressing models, pathogen class models, and make plans for recovery and distribution of models as needed. Humanized animal models were promoted by need to study HIV pathogenesis, e.g., SCID mice engrafted with human tissues. NOD polymorphisms, Rag1, IL2rγ, CD47 deletions also proved useful. Grafts can include ES, iPS cells. Have been used to study many different viruses. Reporter viruses can also be used to study pathogenesis, e.g., via bioluminescence.

Summary (basic research, organ on chip)

Organ on chip: microfluidic device containing living engineered substructures to recapitulate organ dynamics, functionality, and repsonse in vivo. Can include microorganisms.cell lines, primary cells, stem cells. May be used for screening, allowing hypothesis building by dissecting critical factors of human infection, subject to validation in living organisms. Advantages: precision & control, limited immune system via static coculture, human, high throughput & speed, real-time monitoring, low cost. Can model human animal interface e.g., in response to pathogen X & identify disease-related pathways & dissect species-specific differences.

Viral disease infections have been studied iin OoC systems, but need immune system for more complete model. Steps like fusion, immune cell trafficking (e.g., chemotaxis), have been studied. More recently autologous immunocompetent chips (tissue separated from immune cells by semipermeable membrane), bone marrow on chip (with differentiation of myeloid cells on chip), vasculature, recently lymph node on a chip (B cell class switching & plasma cell formation). Linking chips may enable mutiorgan systems. Recent progress on single cell analysis.

Summary (basic research, assays)

WHO assays working group: goal is to improve interpretability of immune assays and enhance access to assay, protein and reagents. Deliberate on assay design & performance, collaborate on protocols, enhance access to reagents/proteins, collaborate on serology standards which facilitated COVID response internationally, e.g., via sharing of success/failure and knowledge, value of platform technologies, development of standards. Recent focus on other priority pathogens. Emphasis for pathogen X on assay platforms for serology & T cells, antigen identification & design, and partnerships & processes for sharing, assay evaluation, and transfer to LMIC facilities.

Summary (basic research, next level)

Understanding everything is important– we don't know where the next pandemic will come from so need to take a broad approach.

Priorities: Standardization to allow widespread deployment of existing technologies. Develop & study broadly cross-protective vaccines (including conserved T cell responses) and antivirals (including passive immunity). Remember limitations of animal models.Response early in pandemic may differ from later (where antivirals, ring vaccination may be more useful early.) Establish regulatory framework to facilitate sharing, including of sequence data. AI may be generalizable tool including for structural analyses, but need to make sure that results (and inputs, including antigens) are reliable. Open access with trained global workforce in public sector, with global/democratized response. Computational infrastructure including data standards that could facilitate collaboration. Research leading to improved surveillance could include migrating birds, contaminated waterways, unexplained illnesses. Global mechanisms to produce & facilitate vaccine deployment in the next pandemic will be important.

Summary (WHO response)

Global agreement to protect against future pandemics is under discussion by member states. Speed and cost of response are important, but quality, equity and trust need to be emphasized for future pandemics. Todays' consultation addressed key research to facilitate pandemic vaccine development, recognizing that other aspects of pandemic response are also important. Pathogen family approach does not reduce importance of individual pathogens– but is complementary and emphasizes value of generalizability, with virus family based TPPs as a key step. Transparency and public consultation will continue, with goal of global consortium to reach these goals.

WHO Hub for surveillance helps provide information to support key decisions as pandemic evolves. Goal is collaborative surveillance that includes strengthened national surveillance, increased capacity (including genomics) and collaborative approaches. Key areas for WHO Health Emergencies Program include governance, surveillance, pandemic & epidemic intelligence, and collaborative intelligence.

WHO Countermeasures network: Following COVID, member state discussions on how to improve access to countermeasures. Focus on supply chains and manufacturing capacity, with further emphasis on greater preparedness in interpandemic period. Pandemic flu, novel coronavirus, pathogen X. Mapping analysis on key questions: where are products in R&D cycle, can we scale up manufacturing rapidly, how would coutnermeasures be equitably allocated, do we have contracts & supply chain in place, and how to scale up delivery.