World Health Organization

Meeting Summary

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A scientific framework for epidemic and pandemic research preparedness
Critical research for priority pathogens with epidemic potential

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R&DBlueprint
Powering research to prevent epidemics

Background

Meeting series focus: how can we prepare based on reasonable predictions, and how can we promote generalizable research focused on prototype pathogens. Where are we, what are the best ways forward to promote development of globally available countermeasures for a future pandemic. This is the second in a series of 4 consultations, today focused on critical research for priority pathogens with epidemic potential.

First meeting 9 January defined scopes of emerging virus threats, discuss generalizable basic research, outline cross cutting scientific actions to address threats from pathogen families regardless of specific potential potential. Discussion included methods for virus detection, advances in antigen design and reagent discovery, strategies for sharing of reagents, ideas, and collaboration.

Prototype pathogen research can speed countermeasure development. Key decision points include antigen design, vaccine platform, safety/efficacy considerations, development pathway/logistics. Ag design: POC, epitope mapping, evolution considerations, breadth/durability considerations. Platforms: extra vs. intracellular Ag delivery, humoral/cellular/mucosal immunity, severe disease vs. spread, prototype experience, scalability. Safety/Efficacy: enhanced disease, platform based considerations, epitope selection. Reg considerations, supply chain including for delivery devices) acceptance. Also: Animal models, clin testing, assay development, process development

Research on pathogen families

Commonalities across virus families: entry mechanisms, enveloped/non-enveloped (different classes of env. glycoproteins). E.g, Ag work on RSV enabled pre-fusion stabiliziation for coronaviruses, platform work may apply to many families. Prototypes may not yield sufficiently broad protection. Platform-based differences may signal immune mechanism differences. e.g., DNA prime can tune response to CD4+ T cells (vs. CD8+ with viral vectors).

Filoviruses: need both humoral and cellular responses.To fully protect,mucosal responses may be important as well. Consider blended, chimeric, sequential approaches to induce broader anti-GP responses, consider NP as key CMI Ag. Potential role of CMI in clearing persistent disease, of Ab in reducing shedding. Survivors have better Fc-dependent responses than vaccinees.

Henipaviruses: (Hendra, Nipah, Mojiang, Langya). Animal reservoirs include bats, shrews, rats. Australia/asia based on animal range. Ag design: Attachment protein G (as in horse subunit Hendra vaccine), Fusion protein F. Vaccine candidates targeting Nipah or Hendra include VSV, mRNA, subunit, Vectored vaccines, F protein deletion, VLPs (including trivalent). Trivalent vaccine to cover bat range (ebola GP, nipah and Hendra F/G). Ab responses may be most important.

Arenaviruses: Ag design is critical for inducing neut Abs. GPC has receptor & membrane fusion domains. Cleavage is critical for trimer formation. Non-covalent GP1 Gp2 complex. Best neut Abs bind to fully condensed pre-fusion trimer. There are 4 neut epitopes, most require GPC (not individual components) which is metastable and heavily glycosylated.GPC-B and GPC-A epitopes defined for Lassa. Now have molecular that can bind/elicit all known epitopes. Need: pre fusion, trimer, native cleavage site

Research on pathogen families

Arenavirus: anti-NP IgM detected in acute phase. 18% case fatality among 1270 lab confirmed cases in Nigeria in 2023. Ig responses develop (average ~1:4 to 1:8 relative to assay cutoff), neuts 1:100 to 1:300 persist at least 1 year. Lineages II, II, IV, VII don't cross-neutralize with Lineage V. NP elicits better immune response than GPC (both cellular and humoral). Low T cell cross reactivity between old world arenaviruses, limited Ab x reactivity with old world arenaviruses.

Alphaviruses (Togaviridae also includes Rubiviruses). ssRNA enveloped infect vertebrates & arthropods. E.e.,g VEE, CHIKV as likely cause of new outbreaks, SIN, MAYV (Mayoro, with some x-rx to CHIKV). Various candidates have been studed in animals, some studied in humans e.g., RRV, VEEV, CHIKV. Some cross protection between CHIKV and EEE. Alphaviruses can be used as viral replicon vectors as well. CHIKV has long-term impact, and vaccine could prevent substantial morbidity. Recently approved vaccine.

How to make research generalizable? Infrastructure: Clinical trial sites preparedness, regulatory environment, labs to do assays. Preclinical work needs to translate to vaccine availability. Identifying key antigens, most appropriate platforms to develop vaccine "systems" is important on a pathogen family level. Stockpiling won't be feasible. Find ways to speed vaccine development after antigen is selected. Rapid response & breadth are both important & linked. Broad spectrum may be more achievable with passive immunity. Multiple vaccines may aid in prime/boost cross clade approach to get broader immunity which may require more than a single prototype pathogen. Broadly protective vaccines may not be feasible for all families. Mucosal vaccines could address many of these needs (but still require the right antigens and development strategies).

Prioritization & Regulation

Choosing between multiple candidates for clinical trials is based on prioritization, availability. Prioritization is an objective process based on scoring by experts.

Regulatory approach to immunobridging: EMA examples. Pre-authorization of flu vaccine based on immunogenicity e.g., vs H5 provides information relevant to future pandemic vaccine with new antigen (feasible in flu because of long experience). COVID approvals allowed new vaccines to be approved for new variants via immunobridging (evidence showed that NAbs from different platforms were protective). Also being considered for filoviruses where protective immune responses have been defined. Some differences between regulators where concepts are evolving. Key considerations: Case definitions & goals, relatedness of pathogens & antigenic similarity, platform consistency, immune & host factors (including CoP/success criteria), assay reliability/standardization, supportive animal data, safety (including potential extrapolation of preclinical studies).

Immunology

Need to understand protection, vaccine effect, population immunity, which require high quality assays. Basic understanding of SARS-CoV-2 immunology facilitated rapid development of reagents to measure immune responses including across variants. Ab responses are important, but T cell responses are more durable and more cross reactive than antibodies which may explain epidemiology of COVID outbreak. Cross reactive T cells can play a role in protection against many other viral families,e.g., Flaviviridae, sarbecoviruses, togaviridae, paramyxoviridae, arenaviridae, picorna/enteroviridae. Importance of measuring humoral, cellular & innate immunity. Standardized assays and reference materials need to be made available.

What have we learned from recent experience?

Broadly protective vaccines made more difficult by antigenic diversity, poor responses to vaccines in the most vulnerable. Major diversity in influenza is in HA and NA. Breadth of protection needs to be considered in context of goals- current flu & COVID vaccines are broadly protective vs. severe disease. Breadth via mixed Ag, broadly reactive Ag, conserved regions, combined platforms.Need lasting mucosal immunity, strategies to subvert immunodominance, induce broadly reactive Ab, learn from MAbs.

Ebola outbreaks are becoming larger & more frequent. V920 (Ervebo) development was collaborative and based on Merck making vaccine available to partners around the world who contributed to its development. Ring vaccination study allowed evaluation of vaccine efficacy in individuals at highest risk.

For flu, stockpiles considered likely enough to have some efficacy. However, in the end, it had little value.

Next steps

Understand the antigenic landscape of pathogens and mechanisms of immunity (Ab and T cells). Better structural definition of non-enveloped & particle viruses to identify key immune response targets on viral surface. Continue work on pathogen family approach including identification of prototypes will help us be prepared. Clinical trials require GMP material. Preparation goals: rapidly ID & characterize virus, rapidly develop & deploy safe new vaccines. Develop new platforms & mucosal vaccines that can induce broadly protective responses. Understand adverse events and vaccine safety. Scale up. Promote science in places where the threats are evolving.

Themes

Importance of basic and translational research in key areas to provide information that will enable rapid development of pandemic vaccines

Antigen design. Rapidly putting prototype vaccines on the shelf won't help if they contain the wrong antigens.

Protective immune responses. Strategies to obtain ***broader*** responses are needed and under investigation– may require vaccines against multiple related pathogens (not just a prototype). Matching platforms to pathogens based on needed immune responses. Also, we need better platforms that could prevent infection/transmission in addition to disease e.g., mucosal vaccines (including strategies for evaluation). Need to understand protection, vaccine effect, population immunity, which require high quality assays.

Manufacturing including scale-up.

Regulation: Regulators are open to extrapolating information from a prototype pathogen to related pathogens within a family. Regulators collaborated extensively during COVID & Ebola vaccine development efforts.

Themes

Unpredictability: Whatever preparation we do, it will likely be impossible to have an effective vaccine on the shelf at the start of the next pandemic. Stockpiling for flu has been futile (though GMP material is needed for clinical studies). Pre-pandemic responses will need to support finding the right antigen once the pathogen is known, and post-pandemic responses on obtaining information needed to demonstrate that the right antigen has been selected and that vaccines are safe.

Context. Consider vaccine development strategies in context with antivirals, and other countermeasures for each family

Collaboration and harmonization increase credibility of all decision-making, and can speed results

Values: Equity, Trust, Quality are as important as Speed and Cost.