Johns Hopkins CEIRS

The Johns Hopkins Center for Excellence in Influenza Research and Surveillance

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Advancing Influenza Research on a Global Scale for the Benefit of Medicine and Public Health

The Johns Hopkins Center for Excellence in Influenza Research and Surveillance (JH-CEIRS) is committed to developing cutting-edge research that helps improve the ability of medical institutions, public health agencies and government institutions to plan and respond to pandemics.

The center will focus on broad influenza surveillance and characterization of virus strains and development of pathways and approaches to rapidly link basic research findings with clinical and public health practices to better prepare for seasonal and pandemic influenza outbreaks.

Projects will include:

- Development of a multi-disciplinary surveillance network which will advance innovative tools and algorithms for rapid molecular surveillance for human respiratory pathogens, including those with pandemic potential
- Identification of viruses with pandemic potential and advancement of our understanding of the impact of virus variants on human disease
- Assessment of the evolutionary potential of influenza viruses via innovative ultra-high throughput microfluidic methods
- Application of robust global modeling methods to evaluate the effectiveness of various public health intervention strategies for pandemic planning and response
- Preparation of plans and tools informed by JH-CEIRS research to assist in the event of a pandemic and complement public health response efforts

Surveillance

Surveillance – U.S. National Capital Region

This human surveillance project will conduct robust active and passive surveillance of symptomatic and asymptomatic patients from the Johns Hopkins Hospital and its affiliated clinics and hospitals in the U.S. National Capital Region. This domestic influenza surveillance network will provide a pipeline for rapid identification of circulating influenza viruses - including those with pandemic potential - in human populations. Human samples will be systematically collected from domestic populations at increased risk for influenza and influenza-related complications and will be coupled with demographic, clinical and epidemiologic data for downstream analysis.

Key Features

- Centrally organized by investigators at The Johns Hopkins Hospital Emergency Department with sampling from both outpatient and inpatient settings, as well as affiliated clinics and hospitals from The Johns Hopkins Health Care System to ensure a robust and comprehensive picture of circulating influenza viruses in National Capital Region patient catchment area.
- The Johns Hopkins Health Care System has an established network and infrastructure for clinical translational research with established pathways for specimen and human subjects data chain of custody. The study is designed to maximize both sample and patient related data collection in an efficient and streamlined manner.

Relevant Past work

- Dr. Richard Rothman and Dr. Andrea Dugas will lead this work; both are highly experienced in human subjects research with expertise in influenza surveillance serving as co-PIs on a contract from The Biomedical Advanced Research and Development Authority - Influenza Diagnosis, Treatment and Surveillance with Xpert Flu.
- The Johns Hopkins Hospital Department of Emergency Medicine has over 25 years of experience in surveillance related research.

Surveillance –Taiwan National Capital Region

Influenza surveillance will also be conducted in South East Asia, at The Chang Gung Memorial Hospital (CGMH) and its regional affiliates. This high density, geographically important region for surveillance will carry out both passive and active sampling will, and include systematic gathering of samples as well as relevant demographic clinical and epidemiologic data.

Key Features

- The influenza surveillance will be systematically performed in three active emergency departments of the same medical institute, the Chang Gung Memorial Hospitals, permitting wide sampling across important geographic regions of Taiwan.
- The CGMH Departments of Emergency Medicine and Infectious Disease serve as an important source of patients care in Taiwan, and have extensive experience setting up "fever centers" during the outbreak of SARS and 2009 H1N1.
- The CGMH is home to The Research Center for Emerging Viral Infections, and has a track record of successful international collaborations. Including those funded by NIAID

Relevant Past Work

- Dr. Kuan-Fu Chen, MD, PhD, the Site Prinicipal Investigator, received his PhD training at and has collaborated with investigators in emergency medicine and infectious diseases at The Johns Hopkins University.
- Dr. Chen has worked with Drs. Rothman and Gaydos, helping to validate the Plex-ID platform for respiratory infections.

Surveillance – Viral Diagnostics and Genome Characterization

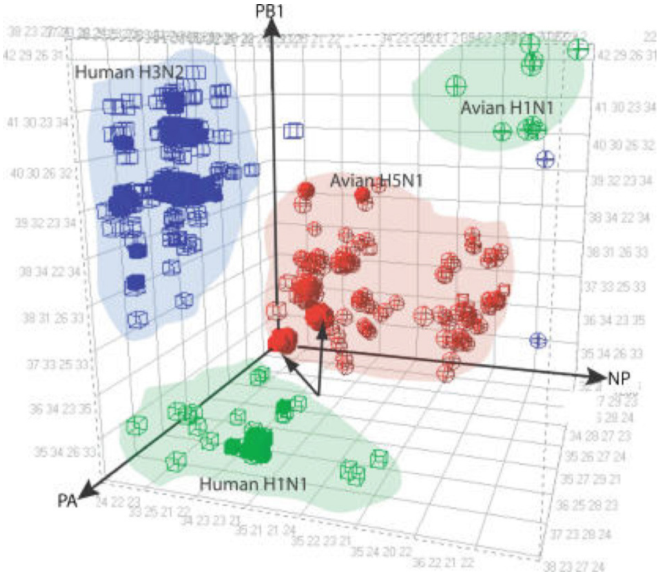
This component of our center will advance an innovative molecular technology, PLEX-ID (Abbott) which utilizes the combined strengths of multiple conserved PCR amplifications, mass spectrometry and a robust bioinformatic software system to provide a rapid detailed genetic fingerprint of the influenza virus strains from an infected individual. This laboratory will provide a program for expedited sorting of influenza specimens and cases into those caused by seasonal influenza (or drift variants of seasonal influenza) versus those caused by a novel genotype of influenza. Influenza positive samples from our surveillance network will be systematically selected and evaluated to identify new, candidate influenza viruses for research in other areas of our center.

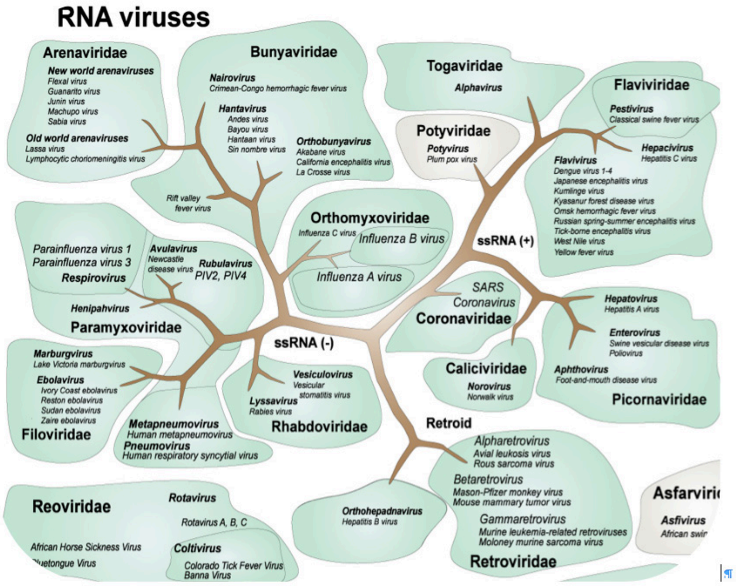
Key Features:

- Program permits rapid screening of large numbers of samples from the United States, Taiwan and other countries around the globe (via Cross-CEIRS collaborations)
- High throughput capabilities and detailed genotyping will permit identification of seasonal variants of influenza, as well as influenza strains with altered disease and pandemic potential

Relevant Work:

- Dr. Charlotte Gaydos and Dr. Rothman participated in early studies which aided in development of PLEX-ID and helped prove that it can distinguish different influenza virus strains from one another
- Our laboratory served as a key site that provided data for FDA approval of Plex ID for testing for influenza viruses
- Prior work by our team with CDC collaboration, demonstrated capability of Plex ID for detection and identification of changes in influenza viruses from different regions across the United States



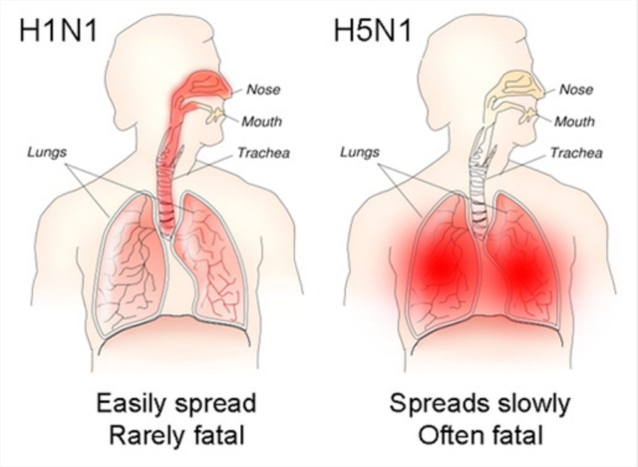


Surveillance – Virus Characterization

This laboratory will evaluate human clinical samples of that are down selected from the genome characterization group, and analyze sequences of influenza virus strains that are associated with enhanced disease. Virus strains will be generated through direct isolation or synthetic biology and be compared to seasonal influenza virus strains both for their ability to infect human respiratory epithelial cell cultures, and their sensitivity to antiviral drugs. This characterization will provide rapid information associated with virus properties that could impact disease severity and help determine pandemic potential of novel influenza virus strains.

Key Features:

- Program allows for characterization of seasonal influenza variants for altered disease potential
- Rapid determination the pandemic potential of novel influenza A virus strains
- Will provide detailed, rapid analysis of virus diversity in human clinical samples



Relevant Work:

- Led by Dr. Andrew Pekosz, a molecular virologist experienced with influenza, hantaviruses and SARS-CoV
- Dr. Pekosz has extensive experience with primary human respiratory epithelial cell cultures under physiologically relevant conditions
- Prior work from this laboratory includes characterization of host and viral factors altering live, attenuated influenza vaccine replication in human respiratory cells

Pathogenesis/Host Response – Influenza-Epithelial Cells

This project will identify the virus sequences that are important for efficient replication in the human upper respiratory tract, via studies in primary human nasal epithelial cell cultures. Since replication in the upper respiratory tract is a necessary, albeit not sufficient, property needed for transmission of seasonal and pandemic influenza A virus strains, viruses will be assessed for their ability to replicate in differentiated and undifferentiated human nasal epithelial cell cultures. The virus sequences that control efficient replication will be determined and virus-infected epithelial cell cultures will be assessed for their ability to function as efficient barriers to infection with selected influenza strains, as well as for their innate immune responses to infection.

Key Features:

- This project will elucidate how virus infection affects human upper respiratory tract epithelial cell function
- Determine key genetic signatures correlating with efficient upper respiratory tract infection
- Investigate epithelial cell repair after virus infection

Relevant Work:

- Dr. Andrew Pekosz’ laboratory has established primary respiratory epithelial cell culture models from human and other animal sources
- This laboratory group has identified mutations in HA that control virus replication in human and mouse respiratory cell cultures

Pandemic Preparedness

Operational

The Johns Hopkins Office of Critical Event Preparedness and Response (CEPAR) will develop plans and tools in the event of a pandemic to include:

- A detailed response plan that is complementary and synergistic with local, national and regional public health response efforts
- Aid coordination among sections and between CEIRS centers and related agencies
- A unified process and a single point of contact for an orderly and effective national-level response

As a leading center in disaster preparedness, a JH-CEIRS response plan would be a model platform for preparing for the emergence of a pandemic. Our response plan to a pandemic would draw upon our nearly decade-long experience in planning for and responding to pandemic emergencies for The Johns Hopkins Health Care System. CEPAR has responded at the national level to several infectious disease events including the Smallpox vaccination campaign, SARS, H1N1 Scarce Resource Distribution, Avian Flu and MERS

Modeling

This project will advance computational models that include both human behavioral responses as well as genomic data of potentially pandemic viruses, to evaluate how a pandemic influenza virus will spread both in physical and genomic space. Combining biophysical properties of the virus with experimental data of potential evolutionary pathways of the virus, will permit prediction of viral fitness (in the presence and absence of various stressors, such as anti-viral medications), and evaluation of the efficacy of select interventions, such as the deployment of vaccines. The models we have range from U.S. national to global in scale. The Global Scale Agent-Based Model (GSAM) and the U.S. only version (LSAM) have been used by NIH, the CDC, and HHS to project pandemic severity for H5N1 and the H1N1 pandemic. That model has also previously been applied to evaluate mitigation strategies, including vaccine and antiviral drug distribution, and social distancing measures - such as closing schools - for purposes of guiding the public health response. Inclusion of viral property parameters in the model will afford enhanced guidance for optimization of intervention strategies in both planning for, and in the event of a pandemic.

Key Features:

- Development of global-scale models of the spread of influenza that include realistic human behavior and travel patterns
- Incorporation of computational biophysics for phylogenetic forecasting with national and global models to aid in predicating the spread of the virus in both physical and genomic space
- Optimization of interventions through model informed planning

Relevant Work:

- The Center for Advanced Modeling in the Social, Behavioral, and Health Sciences, led by Dr. Joshua Epstein, is a world leader in the development of agent-based models

Accelerating Viral Evolution in the Laboratory

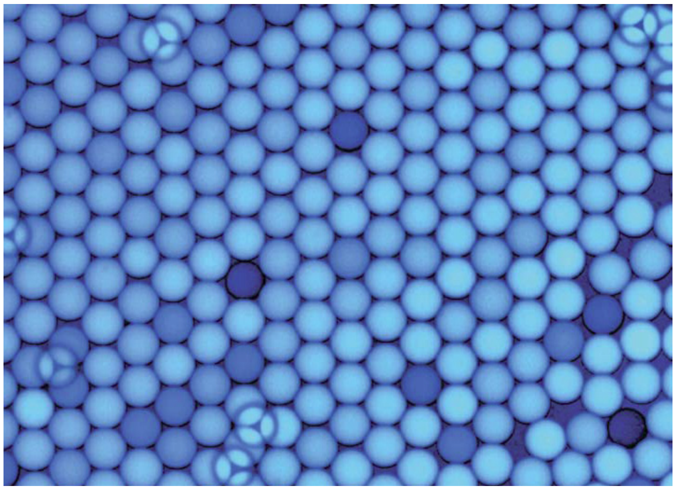
A team including led by Dr. Andrew Feldman at the Johns Hopkins Applied Physics Laboratory (JHUAPL) and consisting of members from JHUAPL, the JHU Emergency Department, JHU Bloomberg School of Public Health and the Harvard School of Engineering and Applied Sciences is exploiting an innovative massively parallel viral culturing technology coupled with epidemiological modeling to predict potential influenza outbreak severity to enable evidence-based pandemic response planning. The culturing system will accelerate the evaluation of potentially dangerous mutations in circulating influenza viruses identified as novel by the JHU CEIRS surveillance effort. The research will result in estimates of the probability that an influenza virus strain might evolve drug-resistance or soon evade population immunity. Laboratory estimates of transmissibility and virulence for potential "future" viruses will inform epidemiological models to assess pandemic risk, as well pandemic response plans.

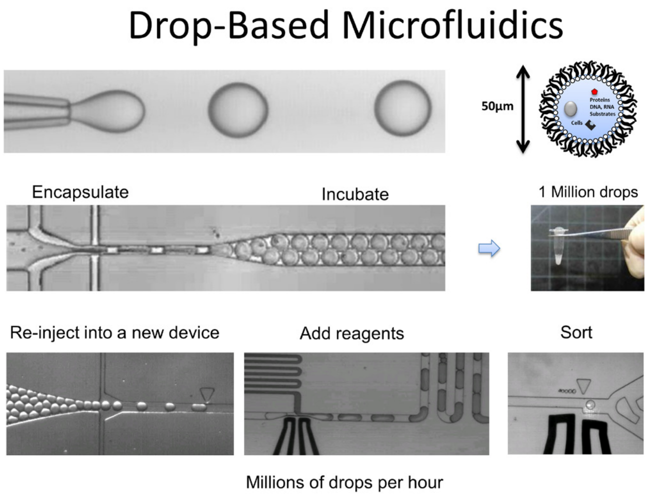
Key Features:

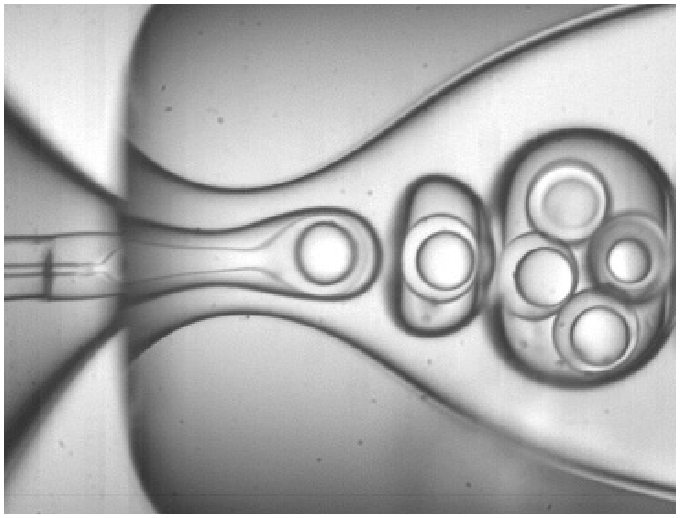
- The microfluidic culturing platform allows for creation of billions of independent trials of virus evolution in ~1 week in the laboratory
- These experiments can predict the evolutionary accessibility of dangerous mutations - such as those conferring drug resistance
- The pandemic potential of mutations will be estimated using detailed epidemiological computer models to assess potential dynamics and severity of influenza outbreaks for the selected virus

Relevant Work:

- A serial-passaging, viral-evolution microfluidics chip was developed and validated under funding from the Defense Advanced Research Projects Agency
- Biophysical models of viral capsid thermal stability and antibody binding have been incorporated in computational global epidemiological models enabling prediction of evolving influenza phylogenies during a simulated outbreak
- Novel bioinformatics methods have been developed to characterize viral quasi-species populations from NexGen DNA sequencing systems







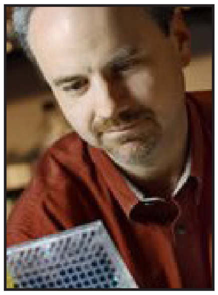
Center Leadership

Richard Rothman, M.D., Ph.D.

Dr. Rothman, Co-Director of JH-CEIRS, is a Professor and Vice Chair of Research for the Johns Hopkins University Department of Emergency Medicine where he also holds a joint appointment in The Department of Medicine, Division of Infectious Diseases. He received his B.A. from Amherst College, Ph.D. from The University of California, San Francisco, and an M.D. from Cornell University. Dr. Rothman has over 20 years of experience conducting research focused on infectious disease surveillance, diagnosis and management at the acute care interface, and development and application of novel rapid molecular diagnostics for infectious disease use. He has extensive experience in leading multi-disciplinary research teams focused on advancing novel approaches for infectious disease surveillance, diagnosis and pandemic planning (funded by grants, contracts and cooperative agreements, from NIH, CDC, DHS and industry). Dr. Rothman is currently Co-Principal Investigator on another multi-center national grant from The Department of Health and Human Services, Biomedical Advanced Research and Development Authority (BARDA) studying implementation of rapid diagnostics for influenza in EDs across the U.S and recently served for more than a decade as the PI for the Diagnostic Program for the Mid-Atlantic Regional Centers for Excellence (MARCE) in Biodefense and Emerging Infectious Diseases (NIAID). He has received numerous grants and awards including the Society for Academic Emergency Medicine Young Investigator Award and the Clinical Scientist Award from the Johns Hopkins University.

Andrew Pekosz, Ph.D.

Andrew Pekosz, Co-Director JH-CEIRS, received a B.S. from Rutgers University and a Ph.D. from the University of Pennsylvania. Dr. Pekosz joined the Department of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health as an Associate Professor in July, 2007. He is a leading expert on the basic biology of influenza and other emerging virus infections and has been interviewed on the topics of influenza and pandemic preparedness by a number of news agencies including National Public Radio's the Diane Rehm Show, the Associated Press (AP), the Baltimore Sun, the New York Times, the Washington Post, Cable News Network (CNN), CSPAN, British Broadcasting Company (BBC), France24, Voice of America, the Discovery Channel and numerous local radio and television stations. Dr. Pekosz has been awarded a number of research grants from the National Institutes of Health and other sources, has authored more than 60 scientific papers, is on the editorial board for several journals and has served on a number of National Institute of Health scientific and policy review boards.



Lauren Sauer, M.Sc.

Lauren Sauer is the executive director of the JH-CEIRS. She also serves as a research associate in the Department of Emergency Medicine where she studies quality of aid in response to disasters and the effects of disasters on healthcare infrastructure. She is also a Core Team Leader on the Johns Hopkins Go Team, a deployable Medical Asset. She has authored and co-authored numerous publications in disaster medicine, public health preparedness and surge capacity metrics ad serves on the editorial board for two disaster journals.

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