over the first 6 months of infection. Discussion will focus on how these results, together with the studies investigating new immunogens may direct more effective design of HIV-1 T cell vaccines. Supported by the NIAD Center for HIV/AIDS Vaccine Immunology grant # U19 AI067854.

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17.003

Understanding Anti-HIV Antibody Targets

P. Moore[1,*], E. Gray[2], M. Madiga[2], N. Ranchobe[2], B. Lambson[2], M.-R. Abrahams[3], G. Bandawe[3], D. Sheward[3], R. Thebus[3], K. Mlisana[4], S. Abdool Karim[4], C. Williamson[3], L. Morris[2]

[1] *Johannesburg, South Africa*
[2] *NICD, Johannesburg, South Africa*
[3] *Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa*
[4] *Centre for the AIDS Programme of Research in South Africa (CAPRISA), University of KwaZulu Natal, Durban, South Africa*

HIV-1 subtype C viruses elicit potent but highly type-specific neutralizing antibodies within the first year of infection. In order to determine the specificity and evolution of these autologous neutralizing antibodies, we examined neutralization escape in four individuals infected with HIV-1 subtype C from the CAPRISA 002 cohort in Durban, South Africa. Early neutralizing responses recognized a very limited number of epitopes, with antibodies that recognize new epitopes evolving sequentially. In addition, only two regions of the envelope were targeted by these antibodies, suggesting there might be common vulnerabilities in the HIV-1 subtype C transmitted envelope. We have shown that type-specific responses have a short term affect on viral load which is lost with the emergence of viral escape mutants. Factors that contribute to the development of broadly cross-reactive neutralizing antibodies, those which would ideally be elicited by an HIV vaccine, are largely unknown. We have examined the evolution of neutralization breadth in the CAPRISA 002 cohort, and shown that cross-neutralizing antibodies develop in about a quarter of infected individuals by 3 years post-infection. Generally breadth develops incrementally suggesting the possibility that multiple antibodies mediate breadth, and/or that breadth is conferred by the maturation of a single specificity. In one case, the development of breadth could be attributed to a single neutralizing antibody specificity. In the CAPRISA 002 cohort, as well as in a cross-sectional cohort of chronically infected individuals, we have explored the targets of cross-reactive antibodies which mediate breadth using an array of methodologies including peptide and protein adsorptions and the use of chimeric viruses. We have shown that multiple epitopes on the envelope glycoprotein are involved in the cross-reactive neutralization elicited during natural HIV-1 infection, many of which are yet to be determined.

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Prophylaxis to Prevent HIV

P. Ndase[1,*], S. Hillier[2], C. Celum[3]

[1] *Infectious Diseases Institute, Kampala, Uganda*
[2] *Magee-Womens Hospital„ Pittsburgh, PA, USA*
[3] *University of Washington, Seattle, WA, USA*

Even with a growing recognition that HIV doesn't discriminate by race, gender, socioeconomic status or sex orientation, the developing world accounts for 90% of the global HIV burden. Sub-Saharan Africa, which accounts for two-thirds of the global HIV infections, Injecting Drug Users, Men who have Sex with Men, and Commercial Sex Workers bare a disproportionate burden of the HIV epidemic. Recent HIV surveillance studies in African countries at best show stabilization of the epidemic or at worst, slight increases in countries like Uganda.

Clearly, the HIV research community recognizes that additional new biomedical prevention modalities are required to augment existing HIV prevention strategies.

Incidence modeling based on as relatively low efficacy as 30% for a Pre-Exposure Prophylaxis (PrEP) regimen or a topical Microbicide has provides a glimmer of hope based on number of new HIV infections prevented through such new modalities. However, scientists need to prove efficacy for these new regimens first.

Several international collaborations with the developing world have been formed to enable us conduct clinical research that meets international standards. Phase IIB and phase III HIV PrEP and Microbicide trials are being conducted in nine countries globally, involving over 20,000 participants in the various high risk groups and across different HIV transmission routes. Each study is being overseen by regulatory agencies both within the developing and the developed world.

The major lessons learned to date are that; North-South collaborative partnerships are critical to realizing the hope of finding new prevention modalities to be added to the HIV prevention tool kit for the most-at-risk groups. Secondly, with these collaborations, the developing world has developed capacity to conduct of clinical research that conforms to international standards for licensure of new products or change of indication of existing drugs/products in the developing world.

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The H1N1 influenza pandemic (Invited Presentation)

18.001

Historical perspective: Lessons Learned from past Pandemics

D. Morens

NIAID, NIH, Bethesda, MD, USA

It has been exactly 500 years since the first recognized influenza pandemic appeared and spread around the world in 1510. Since that time, at least 13 additional influenza

pandemics have been studied by countless historians, physicians and scientists. Influenza and its complications have been well characterized clinically, much has been learned about pandemic epidemiology, and a lore about influenza pandemic behavior has developed over these past five centuries. This includes ideas about pandemic genesis, pandemic cycling, and pandemic wave-like behavior. However today, in the genomics era, much of what we thought we knew is beginning to unravel, and we are quickly discarding old ideas to replace them with rapidly expanding new knowledge. Pandemic influenza was examined using historical research approaches incorporating modern scientific methods to develop a comprehensive overview.

In recent years we have come to understand that there are at least several different mechanisms by which pandemic influenza viruses may be generated, that pandemic cyclicity is probably partly if not wholly a myth, that pandemics may be regional or global, that for most of the past 500 year domestic animals have played a major role in influenza epidemiology, that wave-like pandemic behavior is not inevitable and probably not wholly a viral property, and that influenza co-pathogenesis with common colonizing nasopharyngeal bacteria probably accounts for most influenza-related deaths.

Much remains to be learned about pandemic influenza, and we can expect an explosion of knowledge in the coming decade. It is truly a time to fasten our seatbelts, because the roller coaster is leaving the platform.

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18.002

The H1N1 Outbreak in Mexico

S. Ponce de Leon

Mexico, Mexico

On April 23rd 2009, health authorities in Mexico informed that a new virus was causing an increasing number of severe pneumonia cases in adults with unusually high mortality. After three weeks of intensive clinical and epidemiological research, a new influenza virus was identified as the unknown pathogen in most of the clinical samples sent by Mexico to labs in Winnipeg and Atlanta. The WHO was notified on the night of the 22nd, as soon as the information on etiology was available. At the same time, strict distancing measures were initiated in Mexico City and its suburbs; schools were closed and noncritical activities suspended.

The problem was first evident at the Emergency Room of the National Institute of Respiratory Diseases, and confirmed by simultaneous reports received from San Luis Potosi and Oaxaca. We focused our analysis on cases with severe viral pneumonia and thus overestimated the mortality of the virus during the first weeks of the outbreak — the full picture was apparent only afterwards. The initial response was timely as oseltamivir, educational materials, and protective medical equipment were ready to be sent thanks to Mexico's national preparedness plan for a pandemic. 1340 cases fulfilled the case definition during the first month. Mexico's strict social distancing measures had a significant impact on the number of cases but were later relaxed. The epidemic curve shows a sharp increase, followed by a decrease in the number of cases, with growth during June and July due to a high number of cases in the southeast region. More recently, another wave of increased transmission was present in the metropolitan area.

A significant feature of this outbreak has been the increased mortality in patients between 15 and 55 years old, some previously healthy, with no increase in the young and the old population. Pregnancy and obesity have also been identified as risk factors for severity. Previous immunity probably plays a role in the severity related to age.

Many lessons should be learned from this epidemic: Collaboration, preparedness, transparency, and the importance of being alert towards the unexpected.

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18.003

Global Surveillance of the H1N1 Pandemic

A.W. Mounts

WHO, Geneva, Switzerland

Pandemic surveillance can be viewed from two perspectives, the need to detect the emergence of a novel strain of influenza virus and the need to monitor the progression of spread of the virus. In monitoring pandemic progression, the primary goal is to describe and detect changes in several important epidemiological characteristics of the event. These include severity, both in terms of virulence and impact on society, transmission dynamics, risk groups, and the clinical characteristics and spectrum of disease. Several methods are used for doing this at the global level. These include the existing network of National Influenza Center laboratories through FluNet; monitoring of reports from ministries of health both on web sites and formal submissions; monitoring of media reports, formal communications through WHO country offices and national focal points for International Health Regulations; formal networks of epidemiologists, virologists, and clinicians; and through informal networks of friends, colleagues, and acquaintances. Several shortcomings have been highlighted by the current pandemic including lack of standardization for reporting of a variety of parameters, lack of standard surveillance methods for severe disease, lack of a requirement for reporting of data once initial notification occurs, and the challenge of getting timely data when countries are busy responding to a public health emergency. WHO has proposed a system of sentinel surveillance for severe acute respiratory infections which will be reported country by country onto a global platform which will allow more systematic monitoring of both pandemic and seasonal influenza.

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