The first WHO integrated meeting on development and clinical trials of influenza vaccines that induce broadly protective and long-lasting immune responses

24 – 26 January 2013, Hong Kong SAR, CHINA
Meeting Summary: Progress and Knowledge Gaps

Topics

- Broadly protective and universal vaccines
- Vaccines for viruses with pandemic potential
- Vaccines safety and regulatory issues
- Vaccines production strategies
- Adjuvants for antigen sparing and immune enhancement
- Vaccine delivery methods
- New approaches in vaccination
- Clinical trials in risk groups
Broadly protective & universal vaccines

Progress

Antigenic targets for broadly protective & universal influenza vaccines

Computationally optimized HA VLP vaccine elicits protective broadly reactive Ab

Pseudotyped flu as a vaccine for Induction of heterotypic immunity

Immune responses of broadly protective & universal flu vaccines

Re-engineering HA sequences to develop universal influenza vaccines

Development of universal immunogens against H5N1 viruses and beyond

SMART Technology
Broadly protective & universal vaccines

Knowledge gaps

• Define universal vaccines
  – Breadth of protection versus duration
  – Define minimal requirements of efficacy

• Novel potency, clinical and efficacy assays
  – Assays need measure new factors (e.g. ADCC, egress)
  – Standardize assays
  – Use human challenge studies
  – How do you compare different universal vaccines?

• Overlooked targets & strategies
  – Focus in broadly-cross protective antibodies to HA head
  – Use live viruses
  – Focus on route of administration

• What is the clear regulatory pathway?
Vaccines for Viruses with Pandemic Potential

Progress

• Seasonal /pandemic vaccines
  – Synthetic vaccines
  – Antibody landscapes

• LAIV (Ann Arbor) H5N1 and H7: primes for strong boost with subunit vaccine

• LAIV (Leningrad): Phase 1 studies:
  – Remains genetically stable in volunteers
  – Detectable immune response (HI/MN/CD4/8/IgA)
  – LAIV H7N3 and H5N2 generally safe
  – Further clinical trials planned with H5N2 in Thailand
Vaccines for Viruses with Pandemic Potential
Knowledge gaps

- Alternatives to “RBC”-based HI
- Correlates of protection (conventional and novel) to address needs of conventional and novel vaccine strategies
- Standardizing serology assays
- Neuraminidase: diversity, detection, NA content in vaccines
- Predicting antigenic change from sequence data
- Reduce the 6-8 month vaccine time-scale
- Explore LAIV prime → subunit boost strategies
- (risk assessment of animal viruses for pandemic risk)
Multiple studies conducted on maternal influenza immunization and infant outcome studies: risk inherent in pregnancy (low-moderate), risk of flu in pregnant women (moderate), and risk of flu in fetus (very low)

One VE studies in US resulted lower VE (H3N2) in 2011-12, 2nd confirmed VE by vaccination in prior year

Regulatory principles of registration of vaccines by novel approach existing – routine communication among main regulatory agencies to avoid major discrepancy of practice

Narcolepsy occurred - immune mediated groups

Pharmacovigilance: national experience/mechanism existing
Vaccines Safety and Regulatory Issues
Knowledge gaps

• Rapid release and access to data: clinical, epidemiological and research
• Follow up research to explain findings from VE studies
• Correlation of immunogenicity for different risk groups for registration of vaccines by novel approach
• Public-private collaboration on specific issues e.g. research on biological mechanism of narcolepsy
• Maternal influenza immunization: little-no data on children after 6 months
• Funding
Vaccines Production Strategies
Progress

- Cell and recombinant vaccines are being licensed
- Manufacturing is being scaled up for cell and recombinant technology influenza vaccines
  - Demonstrating feasibility of production
- Demonstrations of rapid production for cell and recombinant vaccines
  - Pandemic responsiveness of the technology
- Cell-based and recombinant vaccines may be more antigenically similar to virus circulating in man
Vaccines Production Strategies
Knowledge gaps

• We need better measures of response to evaluate vaccines
  – New correlates of protection beyond HAI & SMN (Non-HA based)
  – Better animal models for assessment of new vaccines

• Do we need to help the immunogenicity of newer purer products
  – Adjuvants or use more antigen?
  – Impact of glycosylation on immunogenicity

• Pathway for approval
  – How will non-HAI/universal vaccines be licensed
  – High cost for large efficacy studies

• How will new products be sustained on the market
  – Can new technology based vaccines be made available broadly
Adjuvants for Antigen Sparing and Immune Enhancement Progress

- **Oil-in-water (MF59)** - insights into mechanisms:
  - Local muscle cell transcription activation, local ATP release, no stimulation of innate immunity at distant level; early cell immune response predictive of subsequent long-term antibody responses;
  - MF59: documentation of breath, and magnitude of response, priming capacity, avidity maturation

- **Saponin (Matrix M/virosome) H5N1 phase 1**: strong dose reduction, (1.5 ug), crossreactivity, high avidity antibodies

- **Cationic liposome-DNA complexes H5N1**: protective in mice HPAI H5; ferret studies planned

- **Branched peptides-tuftsin/alum**: M2e antigen; superior immunogenicity and protection in mice; intranasal administration studies planned
Adjuvants for Antigen Sparing and Immune Enhancement Knowledge gap

- Consider measures to enhance intrinsic immunogenicity
- Constrained by focus on HAI test, wider array of assays needed with rationale in relation to protection
- Enhance predictability of safety and efficacy: explore potential of systems biology
- Vaccine response is particular difficult to assess in humans due to preexisting immunity induced by natural infection and/or previous vaccination
- Current adjuvants mostly targeted at humoral response – can and should we aim at enhancing CD8 responses?
- Can we further improve duration of immunity, which is of particular relevance to broadly protective vaccines.
Vaccine Delivery Methods
Progress

• Tremendous progress with development progressing from animal studies to human studies for several vaccines
• Intradermal vaccines may offer advantages of dose-sparing and increased immunogenicity (in certain populations); 3 intradermal vaccines are approved and marketed
• In animal studies and one Phase 1 in adults, sublingual administration of live-attenuated vaccines appears comparable to intranasal administration. Relative advantages of each approach will need to be evaluated
• Clinical development of influenza vaccines based on adenovirus and MVA as vectors continues to progress; a Phase I study in healthy adults with a simian adenovirus vector vaccine will begin soon
• New ways to evaluate immune responses to LAIVs are underway, including evaluation IgA NW from past efficacy studies of the Ann Arbor-based vaccines.
• Clinical studies for whole virus vaccines administered intranasally continue; adjuvants are required to achieve the desired immune response.
Vaccine Delivery Methods
Knowledge gaps

• For sublingual vaccines, additional formulation work is needed, particularly for the pediatric population
• Develop novel assays focusing on mucosal response is critical
• In the absence of efficacy studies, standardized ways to evaluate immunologic cross-protection will be important in order to compare and evaluate novel vaccines
• The human challenge model is an important tool for evaluating novel vaccines, but greater capacity and standardization is needed
• As novel influenza vaccines are developed, the unique target population or competitive advantages of such products will need to be considered, given the increasing number of influenza vaccines on the market.
The burden of Influenza B is clear. QIV is safe but shows marginally improved immunogenicity compared with TIV, but no data on clinical efficacy.

High dose vaccines provide increased immunogenicity but efficacy is to be determined. Showed increased local reactogenicity but not VAERS signal.

For the development of 5:3 LAIV reassortant vaccine viruses, inclusion of the wildtype NP gene has the potential to offer improved immunogenicity, particularly with respect to provision of contemporary wild type T cell epitopes.

M2KO replication-deficient virus demonstrated immunogenicity, and protective efficacy in mice and should also be able to elicit anti-M2 responses.

Edible vaccines expressed in corn have been developed for animal diseases (swine TGEV). Lactobacilli expressing influenza antigens have been evaluated in a preclinical model. Addition of an oral adjuvant (CT-B) may enhance responses.
New Approaches in Vaccination
Knowledge gaps

- Need for improved strategy to ensure safe, but more broadly immunogenic and cross-protective seasonal vaccines; “a little bit” of adjuvant may be sufficient for broadening of response
- Need for better immune correlates of protection and regulatory pathway for non-traditional vaccine platforms
- Further evaluation of LAIV reassortment process may yield more immunogenic vaccine virus candidates
- More efficacy studies and additional immune correlates of protection (beyond anti-HA, anti-NA and nasal IgA) are needed
- Need more work on novel delivery approaches that can provide capacity for vaccination of global population in a pandemic
Clinical Trials in Risk Groups
Progress

• 2009 H1N1 pandemic has spurred the accumulation of data on epidemiology and risks of influenza, as well as benefits and risk of influenza vaccination in different risk groups
• Higher doses TIV with boosters improve immunogenicity in HIV-infected adults with CD4 >200 and undetectable HIV & single dose showed effectiveness in preventing lab-confirmed influenza. Vaccines are not sufficiently immunogenic in HIV+ children and those with advanced HIV
• Influenza vaccination is strongly recommended in high risk children and active recall system should be useful. Evidence of vaccine effectiveness is required to convince parents to vaccinate high risk children
• Identification of common best methods and cross-national collaborations in observational studies is in progress to allow pooling of data for improved ongoing global estimation of influenza vaccine effectiveness
Knowledge of disease burden and vaccine effectiveness studies in low income, resource poor countries are urgently needed. Need to look at vaccines as a tool to demonstrate the burden of disease in these countries.

More immunogenic and efficacious vaccines may be needed for patients with advanced HIV and in pediatric HIV patients. Adjuvanted vaccines should be considered. Antibody may not be surrogate for VE in HIV+ adults.

More studies on immunogenicity, safety, efficacy and correlates of protection of influenza vaccines in children and high risk groups are needed. Universal vaccination in pediatric groups can reduce disease burden in high risk children.

Need harmonized methods to define best outcomes, effect of prior year vaccination and antigenic match on vaccine effectiveness. More VE studies in pregnant women and elderly are needed to provide scientific basis and cost-effectiveness data for public health decision-making.