Eight WHO meeting on development of influenza vaccines that induce broadly protective and long-lasting immune responses

Anticipated regulatory process for novel influenza vaccines

August 23 and 24, 2016
Sheraton Grand Chicago Hotel, Chicago, USA

Dr. Michael Pfleiderer
Next generation influenza vaccines....

• Better influenza vaccines
  • Higher efficacy
  • Higher effectiveness

• Influenza vaccines with broader specificity
  • Cross protection against non-vaccine (drifted) strains or subtypes

• Universal influenza vaccines
  • Cross protection against any previous, circulating or emerging influenza virus strain or subtype
...should have significantly improved product profiles compared to the present generation of influenza vaccines

- In terms of efficacy
- In terms of effectiveness
- Probably also in terms of safety
  - e.g., LAIVs in children below 2 years of age
HA – based influenza vaccines (monovalent, TIV, QIV), unadjuvanted

• Split, subunit, recombinant
• “Low”, “normal”, “high” dose
  • Very limited efficacy
    • In unprimed populations
    • In classical at risk groups
  • Very limited effectiveness
    • See above
  • Very restricted strain specificity
    • Only limited cross priming potential
• Cannot be significantly improved
HA – based influenza vaccines
(monovalent, TIV), adjuvanted

• Modern adjuvanting systems are helpful to significantly increase efficacy/effectiveness in unprimed individuals but will not necessarily broaden specificity against non-vaccine strains
• No specific benefit in primed individuals
• May be different for non HA- or multi-epitope vaccine constructs
Entirely new vaccine constructs needed

- Numerous concepts published
- Very few being likely to meet one or more of the requirements defined for better influenza vaccines
  - Reference is made to WHO’s current draft concept on preferred product characteristics (PPC) for better influenza vaccines
Required/expected mode of action (I)

- Effective immune response against multiple viral components facilitating virus neutralization
  - Strain/subtype specific epitopes (better)
  - Conserved epitopes (broader)
  - Stable epitopes (universal)
- Rationally designed and genetically engineered constructs more likely to meet these objectives compared to natural virus antigens
- Live viral vectored constructs expressing novel antigenic structures more likely to meet these objectives compared to classical LAIVs
Required/expected mode of action (II)

- Prime-boost concepts using different vector/delivery systems with the same or a similar antigenic construct probably most likely to be successful
  - Recent examples
    - Ebola candidate vaccines
    - Dengue (candidate) vaccines
    - LAIV/TIV H5N1 vaccine constructs
    - Numerous experimental vaccine concepts
      - Coding nucleic acid/proteinaceous antigen
Regulatory background

- Current guidance not really applicable to novel influenza vaccines
- Too much focused on HA-based seasonal or pandemic vaccines
- Revised EU guidance for influenza vaccines at least considers non HA vaccines
- A lot of scientific and regulatory advice to be provided to developers and manufacturers
- Commonly agreeable guidance desirable
Regulatory requirements for „better“ influenza vaccines

• First licensure
  – Full quality package
  – Full non-clinical package
    • Proof of concept (better, broader, universal)
  – Efficacy
    • Immunogenicity trials
    • Efficacy trials
  – Effectiveness (one season, multiple seasons, “forever”)
    • Functional surveillance systems needed
Immunogenicity and safety

- Unprimed individuals
- Primed individuals
- Dose
- Number of doses
  ..........needed for primary immunization
- Concomitant use with other vaccines
Assays

• No correlates of protection available or likely to be developed on a short term basis
• HAI probably not the most indicative assay
  – Depending on the vaccine construct
• Epitope specific assays
  – Multiple assays needed
• Overall neutralizing capacity of the immune response
• Cell mediated immune response
  – Relevance of readouts from respective assays
Safety and efficacy studies

- All age and risk groups
  - Primary clinical endpoints:
    - Prevention of influenza infection
    - Prevention of influenza disease
      - Prevention of severe disease
      - Prevention of any disease
  - Secondary clinical endpoints:
    - Efficacy against matched strains
    - Efficacy against mismatched strains
- Across several seasons
Effectiveness studies, pharmacovigilance

• Appropriate surveillance systems needed
  – Continuous post marketing surveillance depending on the prophylactic claims made and the target population selected
  – Identifying drift variants escaping from the immune response induced by the vaccine construct used
  – Identifying the need for revaccination
  – Long term safety
Revaccination required?

- When needed?
- Why needed?
- Same vaccine construct sufficient for effective booster response?
- Modified version needed of construct used for primary series?
  - New vaccine?
  - New licensure?
  - New regulatory concept?
- Other vaccine needed for efficient booster response?
Specific needs of LMICs

• Efficacy/effectiveness regarding
  – Circulating strains
  – Mismatched strains
  – Unusual virus circulation patterns
• Overcoming seasonal revaccination
• Effective pandemic priming
Where to conduct clinical trials?

• For use in industrialized countries
  – According to standard rules and procedures
    • Immunogenicity
    • Efficacy
    • Effectiveness

• For use in LMICs
  – Confirmatory immunogenicity studies
    • Comparable immunogenicity = comparable efficacy?
  – Region specific efficacy studies
  – Effectiveness
Study design (I)

• Comparative immunogenicity studies
  – New constructs most likely not comparable to HA-based vaccines
    • Different serological assays required
    • Virus neutralization assays most important
• Pivotal efficacy trials
  – Against a licensed product (LAIV, QIV, TIV)
  – Across several seasons (depending on the claim)
    • Might require seasonal revaccination of the control group
Study design (II)

• Non-inferiority
  • Matched strains
  • Mismatched strains

• Superiority
  • Matched strains
  • Mismatched strains

• Specific safety considerations
  • Stable or changing benefit-risk-ratio
    – Continuous efficacy/effectiveness
    – Waning efficacy/effectiveness
Next steps

• Identify the most promising next generation influenza vaccine(s)
• Identify elements of such vaccine(s) that match with the WHO PPC concept, e.g.
  – Better, broader, universal
    • Any influenza disease
    • Severe influenza disease
  – Suitability/affordability for LMICs
    • General population
    • Children
    • Risk populations
• Develop widely agreeable pathways/guidance to licensure/WHO pre-qualification
Many thanks for your attention