Production of Influenza Vaccines from Reassortants derived from Avian Influenza Viruses: An Interim Biosafety Risk Assessment

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Risk Assessment

- **Hazards** - potential to cause harm
  - Very severe, severe, moderate, slight, negligible

- **Risks** - likelihood of harm occurring
  - Very likely, likely, possible, unlikely, very unlikely

- **Measures to control the risk**
- **Genetically Modified Organism needs environmental risk assessment**

Reference Vaccine Virus Development in WHO Laboratory

Generation of reassortant from HP avian virus and pathogenicity testing

- Hazards
  - Highly pathogenic avian virus
    - Very severe
- Likelihood of harm
  - Very likely
- Control of risk
  - BSL 3+ or 4

After passing pathogenicity tests

- Detailed risk assessment needed

Vaccine Pilot Lots

Potential hazards to human health

- Recipient virus
  - –PR8
- Inserted gene products
  - –NA and modified HA from HP avian virus
- Alteration of pathogenic traits
  - – Receptor specificity
    - experience with H5N1, H9N2 and H7N7

Vaccine Pilot Lots

Potential hazards to human health

- Alteration of pathogenic traits (cont)
  - Removal of HA multi basic amino acids
  - Pathogenicity tests in chickens, ferrets (and mice)
  - Avirulence of PR8 reassortants for man
  - Manufacturing experience with PR8 reassortants
- Potential for transfer of sequences to related micro- organisms
  - Risk of secondary reassortment

Pathogenicity Tests in Chickens

A chicken intravenous pathogenicity test index (IVPI) of 1.2 or less

(OIE, 2001)

Pathogenicity Tests in Mammals

Comparison of reassortant and parental viruses within the same laboratory

- **Ferrets**
  - –Virus replication
  - –Clinical
- **Mice**
  - –Only used when avian virus is pathogenic
  - –Virus replication
  - –Clinical symptoms and LD_{50}

Vaccine Pilot Lots: Likelihood of Harm to Human Health

- It is very unlikely that an Avian:PR8 reassortant is capable of infecting man and causing harm to human health
- If secondary reassortment occurred between the vaccine virus and a human epidemic influenza virus, this reassortant may be replication-competent in man and cause an epidemic

Both these events are very unlikely but preventative measures should be in place

Vaccine Pilot Lots: Environmental Hazards

- It is unlikely that the reassortant vaccine virus will replicate in birds
  - acquisition of 1 PR8 gene abrogates avian virus replication in ducks (Hatta et al, 2002)
  - PR8 virus is attenuated for chickens (Subbarao et al, 2003)
  - H5N1:PR8 reassortants can barely replicate in chickens (Webster, Wood unpublished)
- Pigs and mice may be susceptible

Control measures should be in place

Vaccine Pilot Lots: Assignment of Containment Level and Control Measures

Containment level BSL2+

- Suitable barrier systems
- If barrier systems not available, use powered full-face respirators with HEPA filters
- Consideration given to antiviral prophylaxis
- Code of practice
  - Limit exposure of staff to reassortant
  - Limit aerosols
  - Safe decontamination

Assignment of Containment Level and Control Measures for Pandemic Vaccine Production

WHO to advise on biosafety

Progress with H5N1 vaccine virus development

Two candidate viruses have been produced:

03-021(SJRL), NIBRG-12 (NIBSC)

- Molecular motif for H5 HA pathogenicity removed
- 6:2 reassortants between PR8, H5 HA (modified) and N1 NA rescued in acceptable Vero cells
- H5N1 reassortants not pathogenic in chickens and ferrets – agreed WHO protocols
- WHO 'Interim biosafety risk assessment' drafted – to be used as a model for vaccine manufacturers
- H5N1 reassortants awaiting vaccine production and clinical trial

What happens next?

- WHO risk assessment is published, following consultation period
- If possible, vaccine manufacturers develop BSL2+ facilities for vaccine pilot lot production
- Vaccine manufacturers seek approval for work
  - –veterinary and/or human health
  - –GMO (in some countries)
- Pilots lots of vaccine are produced for clinical evaluation