



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 LD₅₀



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**