

# SARS VACCINE DEVELOPMENT

**Dr. Marie-Paule Kieny**  
**Initiative for Vaccine Research**  
**World Health Organization**  
**Geneva, Switzerland**

# World Health Assembly Resolution on SARS (26 May 2003)

To mobilize global scientific research to improve understanding of the disease and to develop control tools such as diagnostic tests, drugs and *vaccines* that are accessible to and affordable by Member States, specially developing countries and countries with economies in transition.

# This presentation summarises:

- Results from an ongoing survey that WHO is conducting among leading experts from all continents, including:
  - Experts on veterinary coronavirus vaccines
  - Other vaccine experts (including industry)
  - SARS “experts”
  - Regulatory agencies
- Recommendations made at a meeting organized by the National Institutes of Health (NIH) of the United States of America (Bethesda, 30 May 2003).

# **Key issues that need to be addressed on the development of a SARS vaccine**

- Better understanding of the pathogenesis of SARS and of the nature of the protective immune response
- Diversity and (potential) evolution of the SARS coronavirus
- Safety, immunogenicity and efficacy of different types of candidate vaccines in humans
- Conditions for regulatory approval and licensing
- How to use a future SARS vaccine?
- Resources and international co-ordination

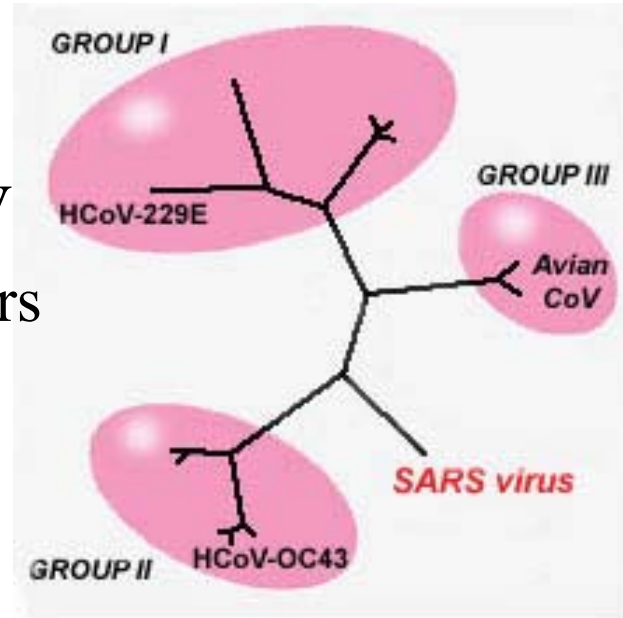
# Issues on SARS pathogenesis relevant for vaccine development

- Role of immune response in SARS pathogenesis?
  - Vaccines against feline coronavirus can trigger antibody-dependent enhancement of disease (not seen with other animal coronavirus infections)
  - Cytokine dysregulation on SARS pathogenesis? (Nichols et al, *Lancet* 24 May 2003).
- Persistence of virus replication and shedding is common
  - What is the mechanism(s) of virus clearance?



# Diversity of coronaviruses

- Three previously known genetic groups of coronavirus cause infection and disease in human and animals:
  - Group 1: Include TGEV (Pig), FIPV (cat), HCoV-229E (human) and others
  - Group 2: Include MHV (mouse), BCoV (cattle), HCoV-OC43 (human) and others
  - Group 3: Include IBV (chicken)
- The SARS coronavirus constitutes a new genetic group (4)
  - Seems to be more related to group 2
  - What is the distribution of this genotype in nature (civet cats, others)?



# Genetic evolution of the SARS coronavirus?

- Coronavirus mutations (especially in gene S) can lead to drastic changes in cell tropism and pathogenicity (Example: In 1984 PRCoV evolved from TGEV).
- Several whole genome sequences (29,751 bases) available
- Need to:
  - Explore genetic diversity of SARS (and SARS related coronaviruses in animals)
  - Monitor continuous evolution of SARS coronavirus

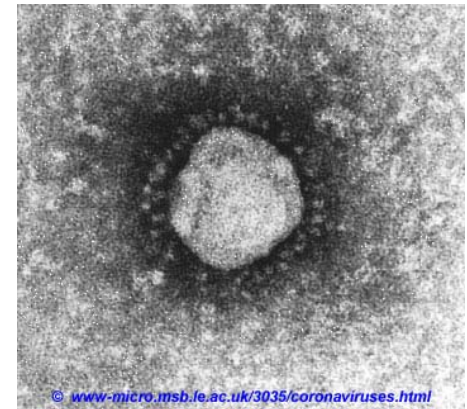
# **Type and duration of immune responses to be induced by SARS candidate vaccines**

- Strong protective immunity may require both humoral and cellular immune responses
- Mucosal immunity may be essential (both in the respiratory and GI tracts).

Human coronavirus (common cold) infection elicits short-lived immunity: reinfection is common after 2 years (although clinical disease is usually reduced).

# Potential types of SARS candidate vaccines

- Whole-inactivated (easier, but perhaps less likely to succeed?)
- Subunit vaccines (Spike protein)
- Vectored vaccines (using Adeno, poxviruses and other viral vectors)
- DNA vaccines
- Combinations of the above
- Live attenuated (more difficult, but perhaps more likely to succeed?).
  - Reverse genetic or Targeted RNA recombination



# Conditions for regulatory approval and licensing

- Vaccine Production
  - Source and quality of starting material
  - Selection/characterization of cell substrate
  - Viral seed history and characterization
  - Validation of manufacturing process for removal and/or inactivation of viruses
  - In process testing
  - Release testing of bulk and final products
- Licensing without phase III data?

# How to use a future SARS vaccine?

- Outbreak reponse?
- Ring vaccination?
- Routine?

# Resources needed for SARS vaccine R&D

- Repository of standardized reagents (virus strains, sera, cells, peptides, molecular clones, etc)
- Databases to guide vaccine development
  - Genetic information (biodiversity and evolution of SARS and SARS-related coronaviruses)
  - Molecular immunology: compendium of T and B cell epitopes (including MHC restriction)
- Animal testing facilities (including primate colonies)
- Biosafety (BSL-3) facilities to work with live virus.

# International coordination

Collaboration needed between:

- Major research institutions (US National Institutes of Health and others)
- Developing countries
- Regulatory Agencies (several critical regulatory issues)
- Industry
- World Health Organization (*Meeting in Geneva, 25-26 August 2003*)

# **Proposed WHO SARS vaccine activities**

- Repository of SARS specimens (virus, sera, cell, molecular clones)
- Database (and continuous analysis) of virus nucleotide sequences
- Collaborative study to standardize laboratory assays for humoral and cell-mediated immune responses
- Studies on SARS immunology and pathogenesis (including mucosal immunity and potential immunopathogenesis issues)
- Address regulatory issues.