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**3Rs in COVID-19 research**  
25 and 26 August 2020 | 3 PM CET

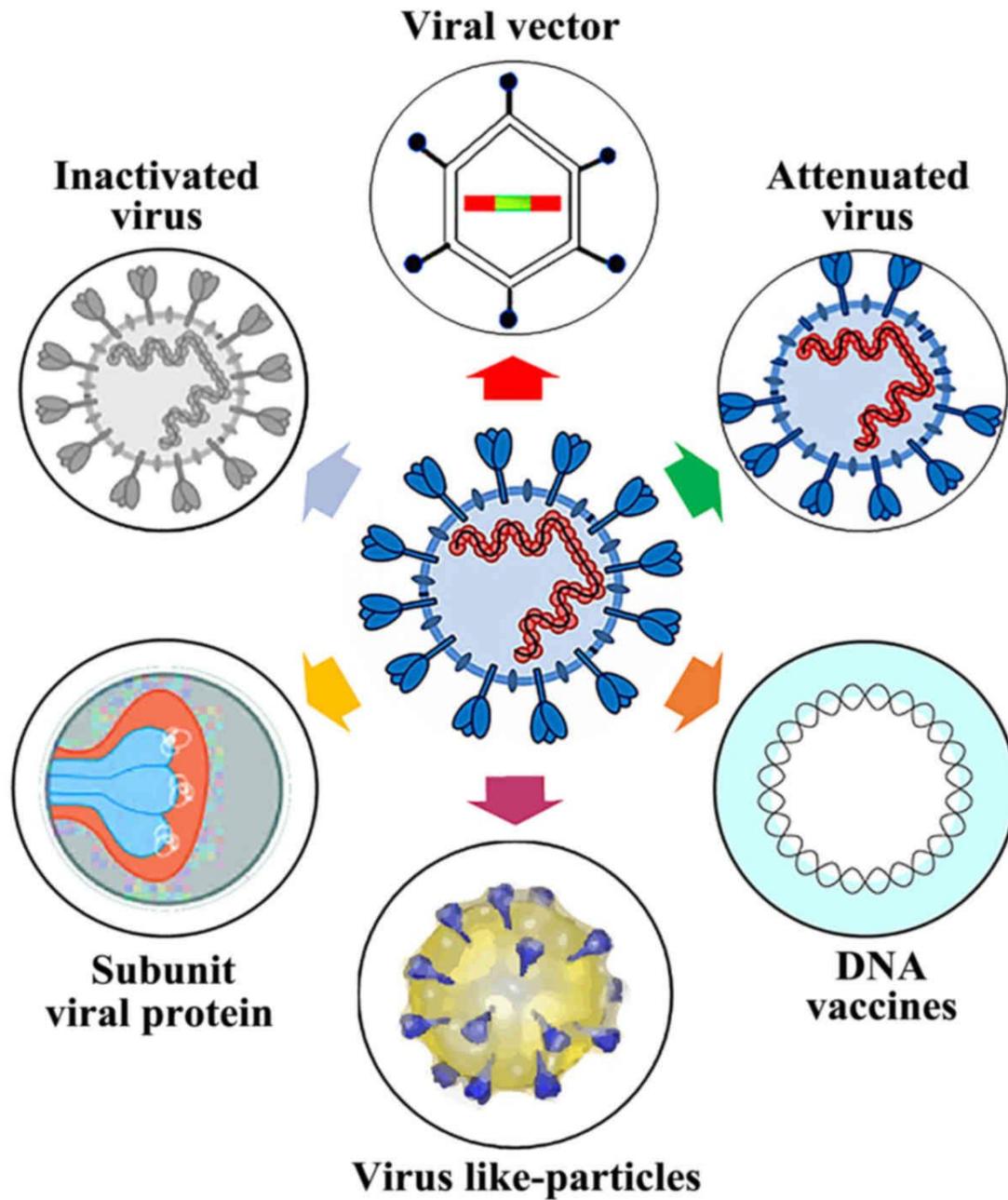
# **3Rs and Covid-19 Vaccine Development: Regulatory Aspects**

**Jan Willem van der Laan**  
**Medicines Evaluation Board**  
**Chair Safety Working Party, CHMP/EMA**

# Viral Vaccine Strategies



- Live-attenuated viruses
  - Measles
  - Rubella
  - Mumps
  - Yellow fever
  - Oral polio (Sabin)
- Recombinant (replicating or non-replicating) viral vector constructs
  - Dengue (based on Yellow Fever-virus)
  - Ebola (based on Modified Vaccinia Ankara or Adeno-associated Virus)
- Inactivated viruses
  - Polio (Salk)
  - Rabies
  - Japanese encephalitis
  - Hepatitis A
- Subunit vaccines
  - Influenza
  - Hepatitis B
  - Human Papilloma Virus as VLP (GSK)



Various  
approaches  
possible

# Animal testing of vaccines before 1990



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- Animal experiments as batch release testing
  - Potency testing
  - Abnormal Toxicity
  - Sensitising potential
  - Immunogenicity
- Adjuvants: No separate issue
  - Aluminium hydroxide,
  - Aluminium phosphate

Old-fashioned  
approaches for vaccine  
testing

# Guidance documents on nonclinical testing of vaccines



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- EU Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines CPMP/SWP/465/95
- FDA Considerations for Developmental and Reproductive Toxicity studies for Preventive Vaccines for Infectious Disease Indications, Final 2007
- WHO Guidelines on preclinical testing of vaccines November 2005
- Guideline on Adjuvants in Human Vaccines CHMP/VEG/17/03, released 2005
- WHO Guideline on Nonclinical evaluation of adjuvants in vaccines, January 2014
- EU Guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines, 2010

General guidelines  
present at WHO, FDA  
and EMA

# Immunogenicity and other Pharmacodynamic Studies



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- Proof of concept
  - Immunogenicity, especially inducing neutralizing antibodies (without challenge)
  - Protecting against postvaccination challenge (if the animal species is responsive)
- Establish immunological characteristics, designed to assess relevant immune responses leading to protection,
  - Th<sub>1</sub>/Th<sub>2</sub> responses
  - T<sub>regulatory</sub> cell response
- Help to select the doses and schedules for First-in-Humans

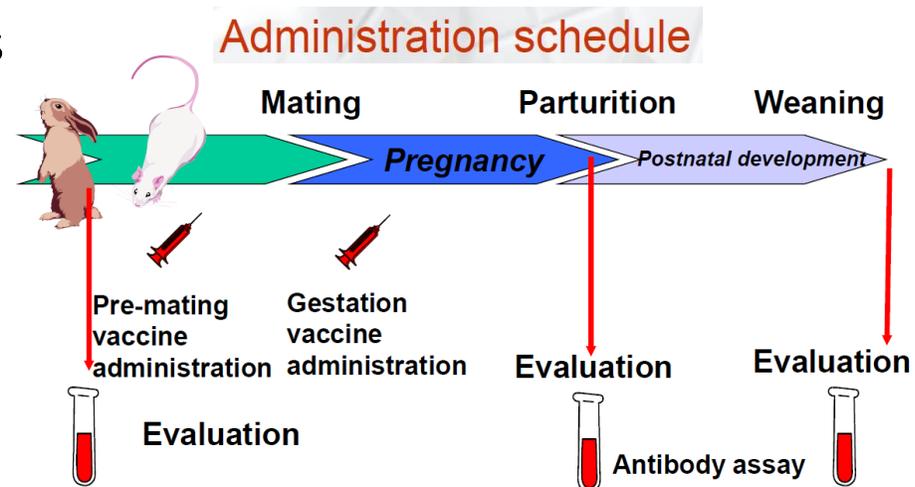
Proof of Concept in a  
Responsive Species

# Safety studies



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- Repeated dose toxicity studies
  - Usually with an N+1 approach (N = intended number of injections)
  - In species with an adequate immune response
  - Maximum dose: Human formulation as the absolute dose
- Reproduction toxicity studies
  - FDA Guidance focusing on maximal antibody response
  - What is the risk?
    - Antibody response or
    - Inflammatory response



From Gruber, 2007

Usually low to absent toxic phenomena

For Safety Testing it is important to have a relevant species as well

# ICMRA Global Regulatory Workshop

18 March 2020



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International Coalition of Medicines Regulatory Authorities (ICMRA) agreed the following positions.

1. The extent of preclinical data to support depends on the vaccine construct, the supportive data available for the construct.
2. Opportunities should be considered to accelerate the development of a SARS-CoV-2 vaccine manufactured using the same platform.
3. If a **platform technology** utilized to manufacture a licensed vaccine or other investigational vaccines is well characterized, **it is possible to use toxicology data (e.g., data from repeat dose toxicity studies, biodistribution studies)** and clinical data accrued with other products using the same platform to **support FIH clinical trials** for a SARS-CoV-2 vaccine candidate.
4. The vaccine manufacturer should justify why certain preclinical studies such as toxicity studies would not need to be conducted prior to proceeding **to FIH clinical trials**.
5. **For all SARS-CoV-2 vaccine candidates it is necessary to obtain data in animals and to characterize the immune response induced by a SARS-CoV-2 vaccine candidate.**
6. It is **NOT** required to demonstrate the efficacy of the SARS-CoV-2 vaccine candidate in animal challenge models prior to proceeding to FIH clinical trials.

Focusing on  
support for  
First-in-Human  
clinical trials

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## Addressing the theoretical risk for SARS-CoV-2 vaccine-induced disease enhancement prior to proceeding to FIH clinical trials

- The potential for **vaccine induced disease enhancement** is a special circumstance that needs to be evaluated according to available science, which may include the use of relevant animal models currently in development.
- It needs to be recognized that there is **limited availability of non-human primates** and requiring such studies with every SARS-CoV-2 vaccine candidate prior to FIH trials is not possible and would significantly delay clinical vaccine development.
- Some vaccine constructs for which there is adequate support from the knowledge around the immune response elicited, may be allowed to proceed to FIH trials without first completing animal studies to assess the potential for enhanced disease provided **adequate risk mitigation strategies** are put in place in these FIH trials.
- In the event that FIH clinical trials are allowed to proceed in the absence of studies in animals that would address the potential for enhanced disease, such studies are, in general, expected to be **conducted in parallel with FIH trials** so that these data are available prior to enrolling large numbers of human subjects into Phase 2 and 3 clinical trials.

Need to  
address the  
theoretical risk  
for vaccine-  
induced  
disease  
enhancement

# ICMRA Global Regulatory Workshop

## 2nd meeting 22 June 2020



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### Preclinical data required to support proceeding to Phase III clinical trials

- Nonclinical data characterizing the vaccine-induced immune response:
  - an evaluation of immune markers of potential enhanced respiratory disease (ERD) outcomes,
  - assessments of functional immune responses (such as neutralizing antibody) versus total antibody responses
  - Th1/Th2 balance.
- Challenge data using nonhuman primates to evaluate the potential for ERD may not be available at the time of Phase III trial initiation. **Preliminary data do not show evidence for a risk of ERD.**
- In general, participants acknowledged **the value of postvaccination challenge data** derived from non-human primates to support proceeding to Phase III clinical trials.
- Data from **other challenge models, e.g. hamsters, ferrets, transgenic mice**, could provide valuable supportive evidence.

Post-  
vaccination  
challenge data  
are still needed  
to support  
Phase III

# WHO- Landscape of COVID-19 candidate vaccines

## 27 July 2020



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### Clinical evaluation

25 candidates with 5 in phase III

- Non-replicating viral vector (1)
- Inactivated whole virion (3)
- RNA (1)

2 candidates in phase II

- Non-replicating viral vector (1)
- Protein subunit (1)

Various  
approaches  
possible  
New approach:  
Nonreplicating  
viral vector.

### Replicating viral vector (such as weakened measles)

The newly approved Ebola vaccine is an example of a viral-vector vaccine that replicates within cells. Such vaccines tend to be safe and provoke a strong immune response. Existing immunity to the vector could blunt the vaccine's effectiveness, however.

### Non-replicating viral vector (such as adenovirus)

No licensed vaccines use this method, but they have a long history in gene therapy. Booster shots can be needed to induce long-lasting immunity. US-based drug giant Johnson & Johnson is working on this approach.

### Protein subunits

Twenty-eight teams are working on vaccines with viral protein subunits — most of them are focusing on the virus's spike protein or a key part of it called the receptor binding domain. Similar vaccines against the SARS virus protected monkeys against infection but haven't been tested in people. To work, these vaccines might require adjuvants — immune-stimulating molecules delivered alongside the vaccine — as well as multiple doses.

### Virus-like particles

Empty virus shells mimic the coronavirus structure, but aren't infectious because they lack genetic material. Five teams are working on 'virus-like particle' (VLP) vaccines, which can trigger a strong immune response, but can be difficult to manufacture.

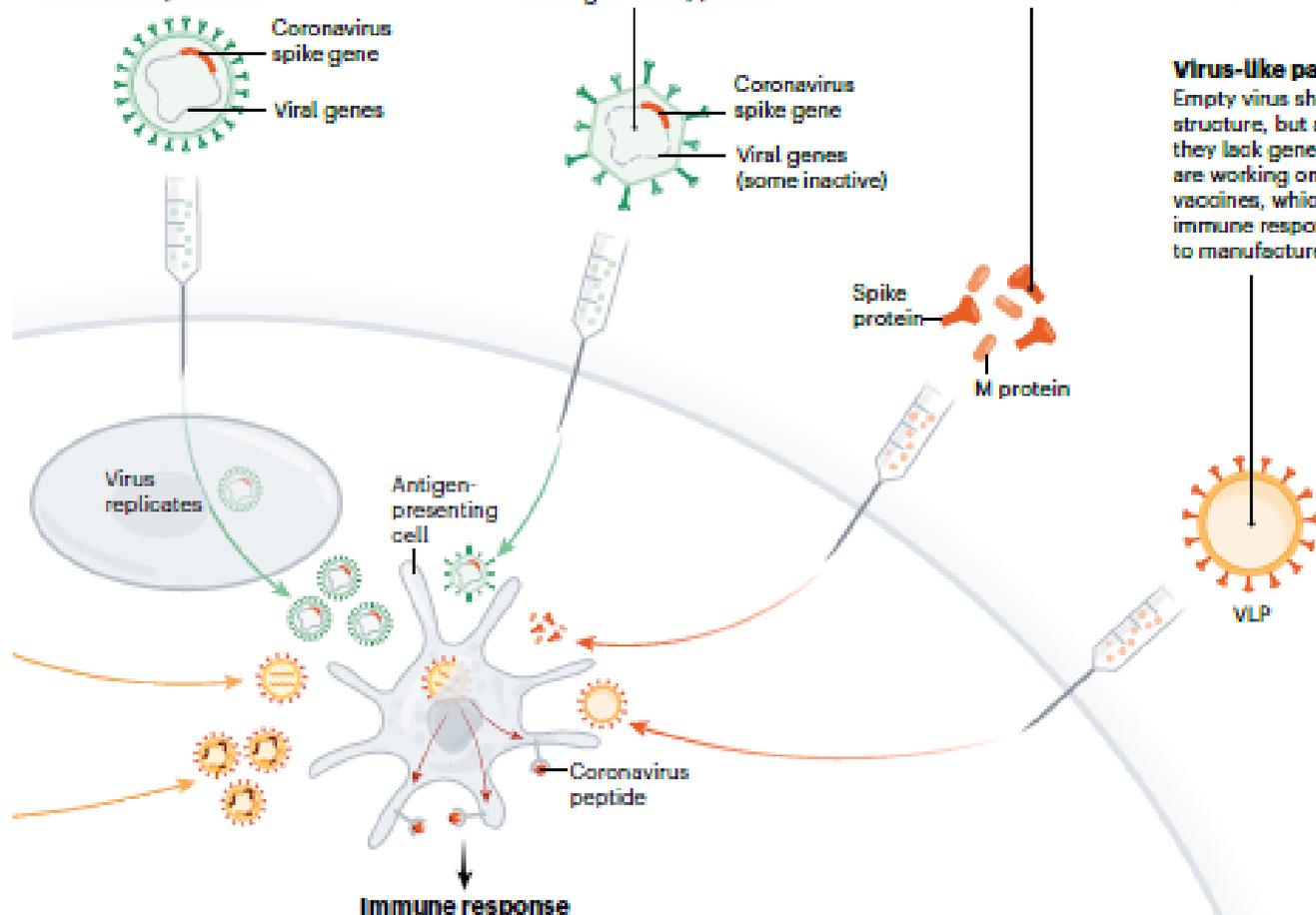


CHART SOURCES: NATURAL ANALYSES BASED ON WHO'S COVID-19 VACCINE LANDSCAPE; MILKIN INSTITUTE COVID-19 TREATMENT AND VACCINE TRENDS; T. HANH LE ET AL. WAREHOUSE DRUG LOGIC: [HTTP://WWW.WHO.INT/PUBLICATIONS/M/ITEM/03032017](http://www.who.int/publications/m/item/03032017); AMANAT ET. US-AEMER IMMUNIZING 31, 383-389 (2020); WU, SHANG ET AL. NATURE VACCINES 5, 18 (2020)



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Various  
approaches  
possible

# Viral vector approach

## **Replicating viral vector (such as weakened measles)**

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Various vector-  
driven  
approaches  
possible

24 June 2010  
EMA/CHMP/VWP/141697/2009  
Committee for Medicinal Product for Human Use (CHMP)

## Guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines

### Section 6.3.1

For the virus from which the vector is derived, **knowledge of its route of infection, of the specific tissues and cells where it replicates, and of the shedding of infectious virus** should be taken into account when determining the strategy for safety testing and help support the relevance of the selected animal model.

Single and/or repeated dose toxicity studies should assess the toxicity of the vaccine compared to formulation control. **Information on the vector itself** without active insert might also be valuable and should be provided

*This type of knowledge of “platform technology” might reduce the need for studies for the product at hand.*

Various vector-  
driven  
approaches  
possible

24 June 2010  
EMA/CHMP/VWP/141697/2009  
Committee for Medicinal Product for Human Use (CHMP)

## Guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines

Other relevant data to be considered:

- 6.3.2. Biodistribution data. Is the incorporation of ‘strange viral’ DNA or RNA influencing the biodistribution, or can we rely on the knowledge for this vector?
- 6.3.3. Reproductive Toxicity data. Consideration should be given to available clinical and/or epidemiological data on infection by the virus upon which the vector is based. Does a heterologous antigen influence the foetus?
  - Transfer of the virus across the placenta
  - Transfer of the antibody-response over the placenta.

*This type of knowledge of “platform technology” might reduce the need for studies for the product at hand.*

Various vector-driven approaches possible

# 3Rs and Covid Vaccine development



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- Reduction of animal use can be applied in first stage of development (no strict need for First-in-Human studies) if data are present from other products with the same platform technology
- Regulatory agreement that studies might be needed to support Phase III, especially post-vaccination challenge studies in NHP. However, availability of NHP might be limited. Other species might be supportive
- Experience with the viral vector during human pregnancy is also very important to consider the need for reprotoxicity studies.



Let's meet at WC11 in 2021!

22-26 August 2021

MECC Maastricht



Questions?