Animal Models to accelerate vaccines development

WHO Network experience during COVID

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To develop and standardize **animal models** to evaluate the potential for vaccine effectiveness and to understand the potential for enhanced disease after vaccination

+379 experts from +20 countries and +60 entities convened since Feb 2020

Live deliberations on **results**
Researchers collaborating on **protocols** and processes
Live state of the art **reviews** to guide developers and researchers
Info on **global capacity** to conduct animal studies

Facilitate access to global resources for **accelerated** evaluation
Enhanced **access** to animal laboratories for **ALL** developers

[https://www.who.int/publications/m/item/global-animal-laboratories-capacities-to-support-vaccine-and-therapeutic-evaluation](https://www.who.int/publications/m/item/global-animal-laboratories-capacities-to-support-vaccine-and-therapeutic-evaluation)
Achievements


Portfolio of models (small/large) to assess pathogenicity, immunity and transmission of SARS-CoV-2

- No evidence of VAERD
- Assessment of VOC transmission and immune escape
- Identification of secondary viral reservoirs

Preclinical development of ALL COVID-19 vaccines
Lessons learned

1) Unprecedented data sharing
2) Sharing failures and successes
3) Avoiding unnecessary repetition
4) Value of pre-prints
5) Standardization
6) ‘Proud to be WHO’
Challenges

1) Animal model repositories
2) Standardization (e.g. hamsters)
3) Lack of immune reagents
4) Animal testing protocols and euthanasia endpoints
5) Moving targets need agility
6) Sharing, sharing, sharing…
SARS-CoV-2 Hamster Disease related to Volume of Intranasal Inoculum


<table>
<thead>
<tr>
<th>Publication</th>
<th>Volume of Intranasal Inoculation (µL)</th>
<th>Specifies per Nare?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenke et al. [3]</td>
<td>50 total (25 per nare)</td>
<td>Yes</td>
</tr>
<tr>
<td>Abdelnabi et al.  [10]</td>
<td>50 total (25 per nare)</td>
<td>Yes</td>
</tr>
<tr>
<td>Kawaoka et al. [9]</td>
<td>30 total</td>
<td>No</td>
</tr>
<tr>
<td>Osterrieder et al. [11]</td>
<td>60 total</td>
<td>No</td>
</tr>
<tr>
<td>Yuan et al. [12]</td>
<td>100 total</td>
<td>No</td>
</tr>
<tr>
<td>Yamasoba et al. [8]</td>
<td>100 total</td>
<td>No</td>
</tr>
<tr>
<td>Huo et al. [13]</td>
<td>200 total (100 per nare)</td>
<td>Yes</td>
</tr>
<tr>
<td>Ryan et al. [14]</td>
<td>200 total (100 per nare)</td>
<td>Yes</td>
</tr>
<tr>
<td>Song et al. [15]</td>
<td>200 total</td>
<td>No</td>
</tr>
<tr>
<td>Zhao et al. [16]</td>
<td>Only PFU provided—cites paper using 100 µL per nare</td>
<td>No</td>
</tr>
<tr>
<td>Sia et al. [17]</td>
<td>Only PFU provided</td>
<td>No</td>
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</table>

Protocols varied from the outset of the outbreak

The IN volume of inoculum proportionally effects disease outcome in the hamster
A moving target needs “Agility”

Viral drift triggered new standards, boosters and reformulation

Omicron drifted away from prototype convalescent immunity

Omicron reduced the efficacy of three doses
Looking at “Pathogen X”

1) Experience can save time and lives (SARS-1, MERS, MPx, Plague, CCHF)
2) Rapid sharing of data, ideas and models will reduce the time to develop vaccines and therapeutics
3) A good understanding of basic pathogenesis and immunology will speed vaccine testing (e.g. T cell epitopes in SARS-CoV-2 spike). Translational approach alone is not enough!
4) We should be prepared in case Disease X is human-specific
CRISPR enabled “required” human elements
<table>
<thead>
<tr>
<th>Genetic status</th>
<th>Wild</th>
<th>-IFN$_{MURINE}$</th>
<th>-IFN$<em>{MURINE}$ +IFN$</em>{HUMAN}$</th>
<th>-IFN$<em>{MURINE}$ +IFN$</em>{HUMAN}$ +Receptor$_{VIRAL}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral susceptibility</td>
<td>Resistant</td>
<td>Susceptible</td>
<td>Susceptible</td>
<td>Susceptible</td>
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<tr>
<td>Infection outcome</td>
<td>Healthy</td>
<td>Lethal</td>
<td>Mild</td>
<td>Severe</td>
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</tbody>
</table>

Add cellular immunity component

Set up multiple human organ MPS
CRISPR enabled "required" human elements

Model Complexity

Model Relevance

Increase complexity of human MPS

Vero cell

Human Multi-MPS

Human Multi-MPS + Immune cells

Human OoC

R&D Blueprint
Powering research to prevent epidemics
Model Complexity

- Known or predicted human threat
- CRISPR enabled “required” human elements
- Increase complexity of human MPS

Model Relevance

- Vero cell
- Human Multi-MPS
- Human Multi-MPS + Immune cells
- Unknown human threat - Disease X
“What needs to be done?”

Sharing data and resources to accelerate development of drugs, therapeutics and vaccines especially standards, reagents, pathology data, clinical samples and methodology.

Simultaneous development of animal models refined for each of the known high-risk groups of pathogens along with simultaneous development of microphysiological systems which may complement or support in vivo approaches.

We should agree ahead of the next event to continue international data sharing