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What are the critical preclinical challenges and how could they be addressed for future candidates before the next pandemic?

WHO R&D Blueprint “Scientific strategies from recent outbreaks to helps us prepare for *Pathogen X*”

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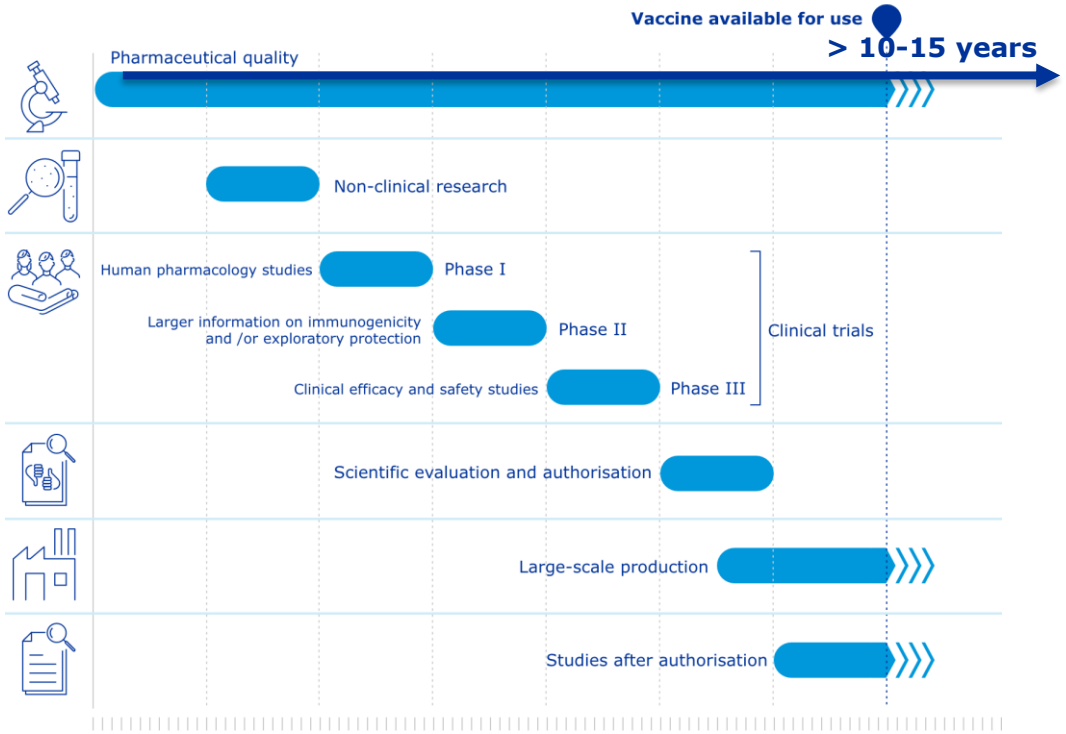
Development of standard vaccines



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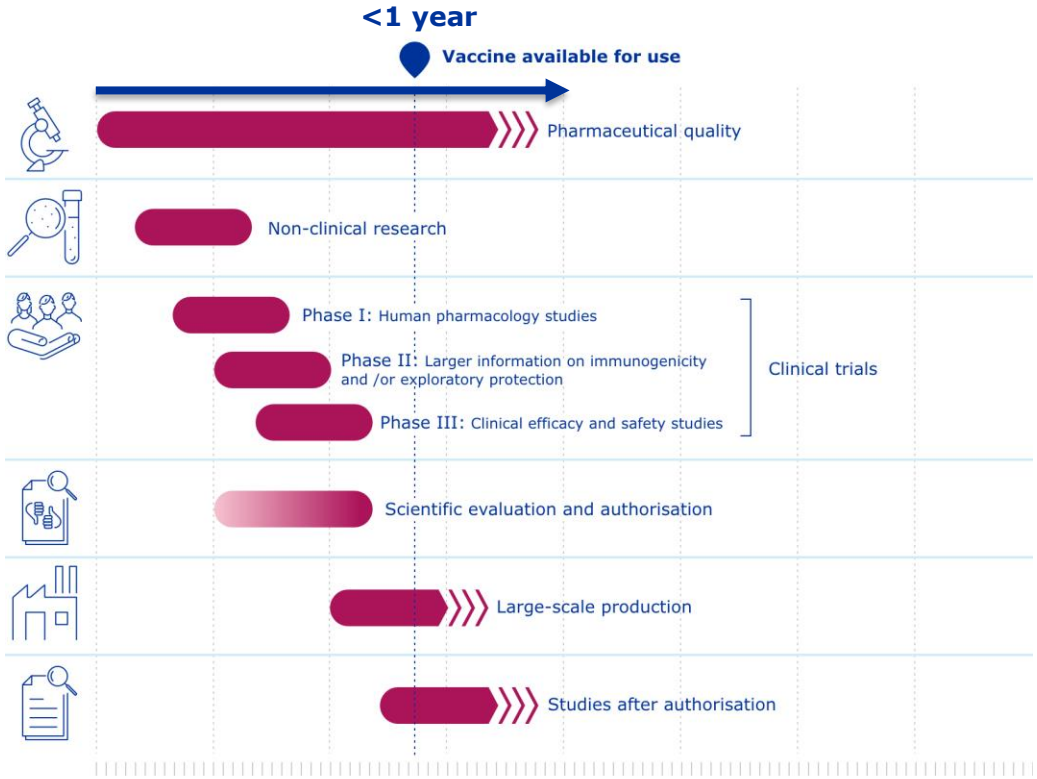
Development of COVID-19 vaccines



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Rapid development of vaccines - COVID Experience

SUMMARY REPORT

Global regulatory workshop on COVID-19 vaccine development

A virtual meeting, held under the umbrella of the International Coalition of Medicines Regulatory Authorities (ICMRA), convening experts from medicines regulatory authorities, the World Health Organisation (WHO) and the European Commission

18 March 2020

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Preclinical data required to support proceeding to First-into-human clinical trials

• The extent of preclinical data required depends on the vaccine construct, the supportive data available for the construct and data from closely related products.

• If a platform technology utilized to manufacture a licensed vaccine or other investigational vaccines is well characterized, it is possible to use data from repeat dose toxicity studies, biodistribution studies from other products using the same platform

•vaccine product characterization and manufacturing should be adequate.

• For all SARS-CoV-2 vaccine candidates it is necessary to obtain data in animals and to characterize the immune response induced the vaccine, but no absolute need for data in animal challenge models

Enhancement of disease with vaccines for other Coronaviruses

- Experiments in animal models (ferrets, monkeys and mice) administered alum adjuvanted inactivated whole cell or VLP, DNA S protein SARS vaccines followed by challenge with SARS CoV showed histopathology in animals administered these SARS-CoV vaccines with a Th2-type immunopathology with eosinophil infiltration

- With MERS-CoV a transgenic mouse model containing the human DPP4 MERS-CoV receptor to evaluate whether Th2-type hypersensitivity immunopathology was observed upon vaccination with an inactivated MERS-CoV vaccine and subsequent challenge with MERS-CoV virus increased infiltrates containing eosinophils in vaccinated groups only suggesting a Th2- type hypersensitivity lung pathology similar to that found with inactivated SARS-CoV vaccines

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Tseng C-T et al (2012) Immunization with SARS Coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus. Plos ONE Vol. 7 (4) e35421

Agrawal et al (2016) Immunization with inactivated Middle East Respiratory Syndrome coronavirus vaccine leads to lung immunopathology on challenge with live virus. Human Vaccines and Immunotherapeutics Vol. 12 (9): 2351-2356

[Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies (nature.com)]

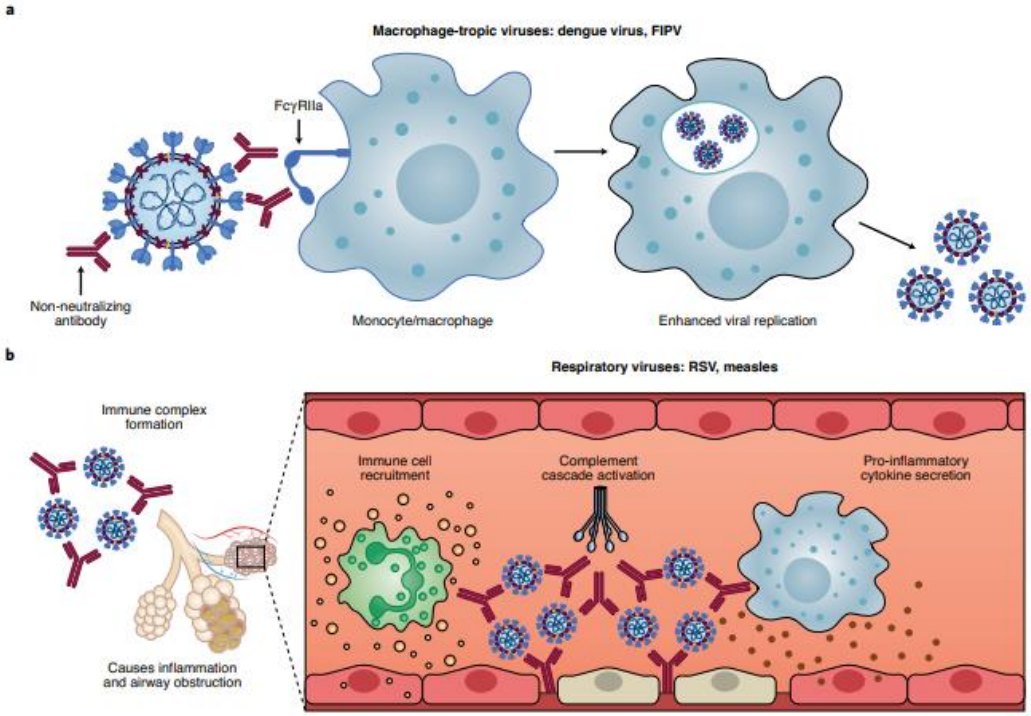

Fig. 1 | Two main ADE mechanisms in viral disease. a, For macrophage-tropic viruses such as dengue virus and FIPV, non-neutralizing or sub-neutralizing antibodies cause increased viral infection of monocytes or macrophages via FcγRIIa-mediated endocytosis, resulting in more severe disease. **b**, For non-macrophage-tropic respiratory viruses such as RSV and measles, non-neutralizing antibodies can form immune complexes with viral antigens inside airway tissues, resulting in the secretion of pro-inflammatory cytokines, immune cell recruitment and activation of the complement cascade within lung tissue. The ensuing inflammation can lead to airway obstruction and can cause acute respiratory distress syndrome in severe cases. COVID-19 immunopathology studies are still ongoing and the latest available data suggest that human macrophage infection by SARS-CoV-2 is unproductive. Existing evidence suggests that immune complex formation, complement deposition and local immune activation present the most likely ADE mechanisms in COVID-19 immunopathology. Figure created using BioRender.com.

Addressing the theoretical risk for SARS-CoV-2 vaccine-induced disease enhancement

• preclinical models with MERS and SARS vaccines candidates pointed to risk of enhancement of disease (ED) and immunopathology.

• Risk was unknown with SARS-COV2 but could not be ignored

• Initial few studies in animal models conducted evaluating the potential for SARS-COV-2 vaccine-induced ED had no clear outcome for ED, but ultimately there was no indication of ED.

• It was reflected that limited availability of non-human primates could significantly delay clinical vaccine development.

• The need to address the potential for vaccine-induced enhanced disease should be based on the totality of available data relevant to the particular vaccine immune response, e.g. Th1-type skewed immune responses, titres of neutralizing antibodies

Animal models that mimic human infection and disease need to be developed

Review

Animal models for COVID-19

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the aetiological agent of coronavirus disease 2019 (COVID-19), an emerging respiratory infection caused by the introduction of a novel coronavirus into humans late in 2019 (first detected in Hubei province, China). As of 18 September 2020, SARS-CoV-2 has spread to 215 countries, has infected more than 30 million people and has caused more than 950,000 deaths. As humans do not have pre-existing immunity to SARS-CoV-2, there is an urgent need to develop therapeutic agents and vaccines to mitigate the current pandemic and to prevent the re-emergence of COVID-19. In February 2020, the World Health Organization (WHO) assembled an international panel to develop animal models for COVID-19 to accelerate the testing of vaccines and therapeutic agents.

Conclusion

- **Platform technology data:** availability of platform technology preclinical data allow rapid start of clinical trials and in some cases, e.g. biodistribution or repeated toxicity data with the same platform but other antigens can replace data with actual antigen
- **Animal models of disease:** importance of having animal models that can de-risk programs, provide answers on specific concerns and accelerate clinical development; however, models can have limitations and may be run by a limited number of labs creating queues and delays in running studies with candidates during emergencies
- **Specific concerns to be addressed:** Enhancement of disease or other specific concerns, e.g. attenuation of live virus vaccines, can be recurrent issues that require rapid data collection from preclinical studies – need to define best approach
- **Other aspects:** preclinical data can support other aspects such as need of adjuvants, narrowing dose ranges for human testing etc, give indication on the type of immune response; importance of the reliability of the immunogenicity testing