World Health Organization

WHO Target Product Profiles for MERS-CoV Vaccines

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Purpose of the document

Selected disease areas are identified as WHO priorities for research and product development. In the case of MERS-CoV, target product profile development followed prioritization of MERS-CoV as part of the WHO R&D Blueprint for Action to Prevent Epidemics. The target audience includes vaccine scientists, product developers, manufacturers and funding agencies.

All the requirements contained in WHO guidelines for WHO policy recommendation and prequalification will also apply. The criteria below lay out some of the considerations that will be relevant in WHO's case-by-case assessments of MERS-CoV vaccines in the future.

None of the characteristics in the tables below dominates over any other. Therefore should a vaccine's profile be sufficiently superior to the critical characteristics under one or more categories, this may outweigh failure to meet another specific critical characteristic. Vaccines which fail to meet multiple critical characteristics are unlikely to achieve favourable outcomes from WHO's processes.

A generic description of WHO's Vaccine Prequalification process can be found at the end of this document.

Modelling of the potential impact of MERS-CoV vaccines with different efficacy profiles and administered using different immunization strategies is a high priority to further refine desired characteristics. Modelling of both camel and human vaccination would be helpful. For certain vaccine characteristics, additional footnotes are provided on the rationale and assumptions made.

Acknowledgement

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I. Background

Middle East Respiratory Syndrome-Coronavirus (MERS-CoV) is an emerging pathogen of increasing importance. As of May 2017, WHO has been notified of more than 1,950 laboratory-confirmed cases of infection and at least 693 deaths related to MERS-CoV. Since September 2012, 27 countries have reported cases of MERS-CoV. [1] The high case fatality rate, large distribution of the reservoir, lack of medical countermeasures, as well as the knowledge gaps in veterinary and human epidemiology, immunity and pathogenesis have placed MERS-CoV as one of the pathogens prioritized in the WHO R&D Blueprint. [2][3] MERS-CoV is important both in its own right, and further as an example of a coronavirus highly pathogenic to humans.

With key stakeholders, WHO facilitated the development of a roadmap for MERS-CoV research and product development.[4] Several priority global research activities were identified to achieve the strategies outlined in the roadmap, including basic, translational, epidemiological and social research; improved diagnostics; therapeutics; monoclonal antibodies (mAbs) and polyclonal antibody preparations and vaccines for humans and dromedary camels.

This document describes the preferred and minimally acceptable profiles for 3 vaccines:

1. Dromedary camel vaccine – for prevention of transmission of MERS-CoV among camels and from camels to humans
2. Human vaccine – for long term protection of persons at high ongoing risk of MERS-CoV such as healthcare workers and those working with potentially infected animals
3. Human vaccine – for reactive use in outbreak settings with rapid onset of immunity

These Target Product Profiles (TPPs) were developed through a consultation process with key stakeholders in human and animal health, scientific, funding and manufacturing communities. It is intended that they will guide and prioritize the development of vaccines. As new scientific evidence is generated, these TPPs may require further review and revision.

Considerations:

Animal Models. An important component of vaccine development is the establishment of animal models that are sufficiently representative of MERS-CoV disease in humans. Small animal models do not reliably represent severe human infection due to the absence of the DPP4 receptor, the human host cell target of MERS-CoV. However, MERS-CoV susceptibility has been demonstrated in mice with transduction of an adenoviral vector expressing human DPP4. [5] MERS-CoV infection in a transgenic mouse model expressing human DPP4 has also been demonstrated. [6] In terms of non-human primate models, it is unclear whether a rhesus or a marmoset monkey model will serve as an accurate predictor of clinical benefit in humans. [7]

Possibility of enhancement. There are some concerns of vaccine-induced pulmonary immunopathology as was observed previously after challenge with SARS virus with a candidate SARS-CoV vaccine in mice[8](although not observed to date in animal models of MERS-CoV). Investigation of MERS-CoV vaccine candidates to induce virus enhancing antibodies and harmful immune response in animal models could be informative before human clinical trials are initiated.

Veterinary vaccines. An animal vaccine strategy may be the best way to prevent human outbreaks and may have the faster development and licensing pathway; however, more resources are required if the dromedary camel vaccination option is to progress. Infection with MERS-CoV in dromedary camels is mildly symptomatic and localized primarily in the upper respiratory tract. The main objective of a camel vaccine is to prevent transmission of MERS-CoV circulation within dromedary herds and prevent transmission from camels to humans. This will require prevention of infection or reduction in viral shedding, which may require mucosal delivery of the vaccine. [9] This indication for use differs from traditional veterinary vaccines. A more workable animal model of upper respiratory tract infection is likely to be necessary to enable development of a vaccine for camels. Recent publications have highlighted the alpaca model in this regard.[10,11]

II. Target Product Profiles

II.A. Veterinary vaccine

Roadmap strategic goal: **Dromedary camel vaccine**: Develop and license a vaccine suitable for administration to camels **to prevent transmission of MERS-CoV between camels and from camels to humans**

Vaccine characteristic	Preferred	Critical or Minimal
Indication for use	To significantly reduce MERS-CoV shedding in dromedary camels and thereby reduce transmission of MERS-CoV among camels and from camels to humans.	
Target population	Dromedary camels of all ages in regions where MERS-CoV camel to human transmission has been documented. Vaccination of dromedary camels imported into regions where camel to human transmission has been documented.	Dromedary camels <2 years of age in regions where MERS-CoV camel to human transmission has been documented. Vaccination of dromedary camels imported into regions where camel to human transmission has been documented.
Safety/Reactogenicity	Must be safe for administration to dromedary camels when administered according to label recommendations. Vaccine must conform to safety standards described in OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals [12]	
	Safety and reactogenicity whereby vaccine has minimal and transient apparent local and systemic adverse events related to vaccination with a low to negligible rate of moderate to serious adverse events related to vaccination.	Safety and reactogenicity whereby vaccine benefit clearly outweighs safety risks. Safety profile demonstrated primarily mild, transient local or systemic health effects and only very rare serious adverse events related to vaccination.
Coverage	Effective in stimulating immunity against MERS-CoV strains that infect camels, with documented protection against clades A and B.	
Measures of Efficacy	Multiple log base 10 reduction in viral shedding in secretions in	90% reduction of MERS-CoV

	camels.	viral shedding in secretions in camels.[1] [2](or one log base 10 reduction)
Presentation	Vaccine is provided as a liquid or lyophilized product in mono-dose or multi-dose (e.g., 10-20 dose) presentations with a maximal dosage volume of 2.0 mL. Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent. Vaccine should be formulated, managed and discarded in compliance with biomedical waste disposal standards. For mucosal delivery, a spray delivery device or means of delivery that does not require special or significant training of qualified vaccinators.	
Dose regimen	Single dose primary series	Up to 3 vaccine doses, preference for short interval between doses and with some protection after first dose. Booster doses: not more frequent than annually.
Durability of protection	At least 3 years.	At least 1 year after last vaccination.
Route of Administration	Spray for mucosal delivery (intranasal).	Injectable (IM, SC).
Co-administration with other vaccines	Data to support co-administration with other vaccines licensed[3] for dromedary camels of the same age groups without significant impact on immunogenicity or safety of the MERS-CoV vaccine or the co-administered vaccines.	The vaccine will be given as a stand-alone product not co-administered with other vaccines.
Product Stability and Storage	Shelf life of 5 years at 2-8^{o}C.	Shelf life of at least 12 months at -20^{o}C, and at least 6 months

[1] Mathematical modelling studies may assist in definition of required percentage of reduction in viral shedding.

[2] The World Organisation for Animal Health is currently developing standard case definition criteria for MERS-CoV disease in dromedary camels, including clinical signs and laboratory confirmation by virus isolation or detection of viral nucleic acid. The MERS-CoV guidance will be made available through this link: http://www.oie.int/en/international-standard-setting/terrestrial-manual/access-online/

[3] Co administration with other licensed vaccines such as camelpox.

	Additional data on thermostability at higher temperatures. Clear label statement to specify storage conditions and expiration. Thermotolerance – supporting data to demonstrate capacity of vaccine to retain satisfactory viability and immunogenicity if frozen or exposed to elevated temperatures during transport or storage. Vaccine Vial Monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container.	stability at 2-8^{o}C. Clear label statement to specify storage conditions and expiration date.

II.B. Human vaccines

1. Roadmap strategic goal: Develop and license vaccine with **long-term protection for administration to those at high ongoing risk of MERS-CoV such as healthcare workers and those working with potentially infected animals**

Vaccine characteristic	**Preferred**	**Critical or Minimal**
Indication for use	For active immunization of persons considered at-risk based on specific risk factors to protect against MERS-CoV. Risk groups will include health care workers (HCW), frontline workers (FLW) and those working with potentially infected animals.	
Target population	HCW, FLW and others with occupational risk. Suitable for administration to pregnant women.	HCW, FLW and others with occupational risk.
Safety/Reactogenicity	Safety and reactogenicity at least comparable to WHO-recommended routine vaccines, providing a highly favourable risk-benefit profile, ideally with only mild, transient adverse events related to vaccination and no serious AEs	Safety and reactogenicity whereby vaccine benefit clearly outweighs safety risks. Safety profile demonstrated primarily mild, transient health effects and rare serious AEs related to vaccination.

	related to vaccination, including in individuals with compromised immune function. Additional pre clinical data showing absence of harmful immune response (i.e., inducement of virus enhancing antibodies).	
Measures of Efficacy	At least 90% efficacy in preventing Middle East Respiratory Syndrome caused by MERS-CoV in healthy adults. Prevention of virus shedding. If regulatory authorization is provided without clinical efficacy data, effectiveness data are to be generated during use in a future outbreak to the extent possible.	At least 70% efficacy in preventing Middle East Respiratory Syndrome caused by MERS-CoV in healthy adults. If demonstration of clinical efficacy is not feasible, pre-clinical immunogenicity and efficacy in a standardized and relevant animal model together with clinical immunogenicity may be considered.[4] [5] If regulatory authorization is provided without clinical efficacy data, effectiveness data are to be generated during use in a future outbreak to the extent possible.
Dose regimen	Single-dose regimen preferred	Primary series: No more than 3 doses, and with preference for short interval between doses. Booster doses: No more frequent than every 3 years or at time of new outbreak. Rapid induction of protective anamnestic response.
Durability of protection	Confers long-lasting protection of 5 years or more following the primary series and can be maintained by booster doses.	Confers protection of at least 3 years after primary series and can be maintained by booster doses.

[4] These considerations should be discussed between manufacturers and regulators early in the development process
[5] An attempt should be made to identify correlates of protection in an appropriate preclinical model.

	Duration of protection may be inferred from immune kinetics, as well as documentation of breakthrough cases.	Duration of protection may be inferred from immune kinetics, as well as documentation of breakthrough cases.
Route of Administration	Injectable (IM, ID or SC) using standard volumes for injection as specified in programmatic suitability for PQ or needle-free delivery. Oral or non-parenteral route desirable	Injectable (IM, ID or SC) using standard volumes for injection as specified in programmatic suitability for PQ. Other routes of administration (including those involving electroporation) would be reviewed by WHO advisory committees related to prequalification and policy recommendation.
Coverage	Protective against MERS CoV strains infecting humans.[6]	
Product Stability and Storage	Shelf life of 5 years at 2-8^{o}C. Additional data on thermostability at higher temperatures. The need for a preservative is determined and any issues are addressed. Vaccine Vial Monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container. Vaccines that are not damaged by freezing temperatures (<0^{o}C) are preferred. Vaccines that can be delivered via the Controlled Temperature Chain are preferred.[7]	Shelf life of at least 12 months at -20^{o}C and 6 months at 2-8^{o}C. The need for a preservative is determined and any issues are addressed. Vaccine vial monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container.
Co-administration with other	The vaccines can be co-	The vaccine will be given as a

[6] Mackay IM, Arden KE. Virus Research, 2015.
[7] http://www.who.int/immunization/programmes_systems/supply_chain/resources/Controlled-Temperature-Chain-FAQ.pdf

vaccines	administered with other vaccines licensed[8] for the same age and population groups without clinically significant impact on immunogenicity or safety of the MERS-CoV vaccine or the co-administered vaccines.	stand-alone product not co-administered with other vaccines
Presentation	Vaccine is provided as a liquid product in mono-dose or multi-dose presentations with a maximal dosage volume of 0.5 mL. Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy.	Vaccine is provided as a liquid or lyophilized product in mono-dose or multi-dose presentations with a maximal dose volume of 1.0 mL. Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy. Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent.
Registration and Prequalification*	Should be WHO pre-qualified according to the process outlined in Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies.[9]	

2.. Roadmap strategic goal: Develop and license single dose MERS-CoV vaccine suitable for **reactive use in outbreak settings with rapid onset of immunity**

Vaccine characteristic	**Preferred**	**Critical or Minimal**
Indication for use	For active immunization of at-risk persons in the area of an on-going outbreak for the prevention of Middle East respiratory syndrome (MERS) caused by MERS-CoV; to be used in conjunction	

[8] Co administration with e.g., inactivated influenza, Tdap, HPV, etc depending on recommended in immunization schedule indicated for target population

[9] http://apps.who.int/medicinedocs/documents/s21095en/s21095en.pdf

	with other control measures to curtail or end an outbreak.	
Contraindication	No contraindication for use in individuals with compromised immune function.[10]	
Target population	All ages.[11] Suitable for administration to pregnant women.[12]	Adults[13], including those older than 50 years old
Safety/Reactogenicity	Safety and reactogenicity sufficient to provide a highly favourable benefit/risk profile in the context of observed vaccine efficacy; with only mild, transient adverse events related to vaccination and no serious AEs. Additional pre- clinical data showing absence of harmful immune response in animal models (i.e., inducement of virus enhancing antibodies)	Safety and reactogenicity whereby vaccine benefits clearly outweigh safety risks.
Measures of Efficacy	At least 90% efficacy in prevention of Middle East Respiratory Syndrome (caused by MERS-CoV) in healthy adults. Prevention of virus shedding. Rapid onset of immunity (less than 1 week). If regulatory authorization is provided without clinical efficacy data, effectiveness data are to be generated during	At least 70% efficacy in prevention of Middle East Respiratory Syndrome (caused by MERS-CoV) in healthy adults.[14] Rapid onset of immunity (less than 2 weeks). If demonstration of clinical efficacy is not feasible, pre-clinical immunogenicity and efficacy in a standardized and relevant animal model together

[10] Severe MERS-CoV cases have been reported in those >50 years old and in those with co morbidities such as diabetes, hypertension, cardiac disease, obesity, chronic respiratory disease, end stage renal disease, pregnancy, cancer or in persons receiving immunosuppressive therapy.

[11] The youngest age reported is 1 year old.

[12] Pregnancy has been documented as a comorbidity in published MERS-CoV case series

[13] Of all laboratory-confirmed cases reported to date, the median age is 52 years (IQR 36-65; range >1-109 years) and 66% are male. About 20% are reported to be health care workers.

[14] Mathematical modelling may inform the percentage of vaccine efficacy that could have a substantial impact on transmission if deployed appropriately during an ongoing outbreak.

	use in a future outbreak, to the extent possible.	with clinical immunogenicity may be considered.[15] [16] If regulatory authorization is provided without clinical efficacy data, effectiveness data are to be generated during use in a future outbreak, to the extent possible.
Dose regimen	Single-dose primary series.	Primary series: No more than 2 doses, preference for short interval between doses and with some protection after first dose.
Durability of protection	Confers protection for at least 1 year. Duration of protection may be inferred from immune kinetics, as well as documentation of breakthrough cases.	Confers protection for at least 6 months.[17] Duration of protection may be inferred from immune kinetics, as well as documentation of breakthrough cases.
Route of Administration	Injectable (IM, ID or SC) using standard volumes for injection as specified in programmatic suitability for PQ or needle-free delivery. Oral or non-parenteral route desirable.	Injectable (IM, ID or SC) using standard volumes for injection as specified in programmatic suitability for PQ. Other routes of administration (including those involving electroporation) would be reviewed by WHO advisory committees related to prequalification and policy recommendation.
Coverage	Protective against MERS CoV strains infecting humans.[18]	
Product Stability and Storage	Shelf life of 5 years at 2-8^{o}C. Additional data on thermostability at higher	Shelf life of at least 12 months at -20^{o}C, and demonstration of at least 1 month stability at 2-8^{o}C.

[15] These considerations should be discussed between manufacturers and regulators early in the development process
[16] An attempt should be made to identify correlates of protection in an appropriate preclinical model
[17] Median duration of 8 healthcare associated MERS-CoV outbreaks (outbreaks with at least 20 cases) was 75 days (20-132 days).
[18] Mackay IM, Arden KE. Virus Research, 2015.

	temperatures. The need for a preservative is determined and any issues are addressed. Vaccine vial monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container.	The need for a preservative is determined and any issues are addressed. Vaccine vial monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container.
Co-administration with other vaccines	The vaccine will be given as a stand-alone product not co-administered with other vaccines.	
Presentation (for parenteral forms)	Vaccine is provided as a liquid product in mono-dose or multi-dose presentations with a maximal dosage volume of 0.5 mL. Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy.[19]	Vaccine is provided as a liquid or lyophilized product in mono-dose or multi-dose presentations with a maximal dose volume of 1.0 mL. Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy. Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent.
Registration and Prequalification	Should be WHO pre-qualified according to the process outlined in Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. [20] Please refer to the considerations for Emergency Use Assessment and Listing Procedure (EUAL) for candidate vaccines for use in the event that MERS CoV is declared a public health emergency of international concern.[21]	

[19] http://apps.who.int/iris/bitstream/10665/135972/1/WHO_IVB_14.07_eng.pdf
[20] http://apps.who.int/medicinedocs/documents/s21095en/s21095en.pdf
[21] http://www.who.int/medicines/news/EUAL-vaccines_7July2015_MS.pdf?ua=1

III. Considerations on Programmatic suitability

IV.A. Vaccine for human use

WHO Prequalification

Vaccines that are procured by United Nations agencies and for financing by other agencies, including Gavi, the vaccine alliance, require WHO Prequalification. The WHO prequalification (PQ) process acts as an international assurance of quality, safety, efficacy and suitability for low and middle-income country immunization programs. WHO encourages vaccine developers and manufacturers to be aware of the WHO prequalification process, even at the early stages of development and to discuss the product and the regulatory requirements with the WHO prequalification staff early in the process. Licensure by a national regulatory authority (NRA), or European Medicines Agency in the case of the centralized procedure for marketing authorization in Europe, will be required prior to any consideration of prequalification. Furthermore the prequalification process requires regulatory oversight by the NRA of Record, which is usually the NRA of the country where the vaccine is manufactured or the NRA of the country of finishing and distribution, and such an NRA should have been assessed as functional by WHO. Vaccine developers should check that the planned NRA of Record for the prequalification procedure is considered functional by WHO.

The prequalification procedure is described in detail in the document Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies (WHO TRS 978) available here: http://apps.who.int/medicinedocs/documents/s21095en/s21095en.pdf.

The WHO PQ process which assesses vaccine quality, safety, efficacy and suitability for use in low and middle-income countries has developed criteria called Programmatic Suitability for Prequalification (PSPQ) criteria to review vaccines submitted for prequalification. (http://apps.who.int/iris/bitstream/10665/76537/1/WHO_IVB_12.10_eng.pdf).

Considerations of Programmatic Suitability for Prequalification

In addition to meeting quality, safety and efficacy requirements, it is also important that developers and manufacturers understand WHO's preferences for parameters that have a direct operational impact on immunization programs. Low programmatic suitability of new vaccines could result in delaying introduction and deployment. In addition, introduction of new vaccines that have higher volume, cold chain capacity or disposal demands have had a negative impact on existing operations of immunization programs. Therefore early stage consideration of presentation and packaging parameters is encouraged. Deferring these considerations may lead to additional costs and delays required for reformulation later in the development pathway.

IV.B. Vaccine for veterinary use

Manufacturing and production of animal vaccines should meet the minimum standard requirements recommended by the World Organisation for Animal Health (OIE). [12]

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