Coronavirus Enhanced Disease Literature Review

APPENDIX A

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#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
1	Whole UV-inactivated SARS-CoV (UV-V) (Iwata Yoshikawa 2014)	Mouse BALB/c	Whole UV-inactivated SARS vaccine that includes nucleocapsid protein is reported to induce eosinophilic infiltration in mouse lungs after challenge with live SARS-CoV. TLR agonists added to UV-V vaccine, including lipopolysaccharide, poly(U), and poly(I·C) (UV-VTLR), reduced excess eosinophilic infiltration in the lungs using 6-month-old adult BALB/c mouse model. CD11bcells in the lungs of UV-V-immunized mice showed the upregulation of genes associated with the induction of eosinophils after challenge.	Vaccine-induced eosinophil immunopathology in the lungs upon SARS-CoV infection could be avoided by the TLR agonist adjuvants.	J Virology doi:10.1128/JVI.00983-14 Effects of Toll-Like Receptor Stimulation on Eosinophilic Infiltration in Lungs of BALB/c Mice Immunized with UV-Inactivated Severe Acute Respiratory Syndrome-Related Coronavirus Vaccine
2	SARS recombinant native full-length Spike-protein trimers (triSpike) (Jaume 2012)	In vitro	Spike envelope glycoprotein (S) is the most significant SARS-CoV neutralising and protective antigen; antibody-mediated enhancement of SARS-CoV infection with anti-SARS-CoV Spike immune-serum was observed in vitro.	Antibody-mediated infection of SARS-CoV triggers entry into human haematopoietic cells via an FcγR dependent and ACE2-, pH-, cysteine-protease-independent pathways. The antibody-mediated enhancement phenomenon is not a mandatory component of the humoral immune response elicited by SARS vaccines, as pure neutralizing antibody only could be developed. Enhanced infection of macrophages following antibody-mediated entry of feline coronavirus is	Hong Kong Med J Vol 18 No 1 Supplement 2 February 2012 SARS CoV subunit vaccine: antibody-mediated neutralisation and enhancement.

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				responsible for the occurrence of deadly feline infectious peritonitis.	
3	Delta inulin-based polysaccharide adjuvanted whole virus and spike protein vaccine for SARS (Honda-Okobu 2015)	Mouse BALB/c	Delta inulin induces balanced Th1 and Th2 immune responses, which contrasts with alum's marked Th2 bias. Recombinant spike protein or inactivated whole-virus vaccine candidates, alone or adjuvanted with either alum, CpG, or Advax, a new delta inulin-based polysaccharide adjuvant in adult female BALB/c mice 6 to 8 weeks of age, While all vaccines protected against lethal infection, addition of adjuvant significantly increased serum neutralizing-antibody titers and reduced lung virus titers on day 3 post challenge. Protection against eosinophilic immunopathology by vaccines containing delta inulin adjuvants correlated better with enhanced T-cell gamma interferon (IFN-) recall responses rather than reduced interleukin-4 (IL-4) responses, suggesting that immunopathology predominantly reflects an inadequate vaccine-induced Th1 response.	Whereas unadjuvanted or alum-formulated vaccines were associated with significantly increased lung eosinophilic immunopathology on day 6 post challenge, this was not seen in mice immunized with vaccines formulated with delta inulin adjuvant.	.doi:10.1128/JVI.02980-14. Severe Acute Respiratory Syndrome-Associated Coronavirus Vaccines Formulated with Delta Inulin Adjuvants Provide Enhanced Protection while Ameliorating Lung Eosinophilic Immunopathology
4	RBD-S recombinant SARS subunit receptor-binding spike (S) protein on alum & GLA (glucopyranosyl lipid A) (Jiang 2012)	Mouse human angiotensin-converting enzyme 2 transgenic (Tg) model (proposed)	Vaccine with alum (either Alhydrogel® or aluminum phosphate), together with a synthetic Toll-like receptor 4 (TLR4) agonist known as glucopyranosyl lipid A (GLA). RBD-S polypeptide formulation, rather than the complete S protein. **It is not clear how much data has been developed with this vaccine in animal models to support the reduced risk of disease enhancement**.	RBD subunit component of the spike protein is highly protective in laboratory animals, while significantly reducing the risk of antibody enhancement of disease (review of previous studies).	doi:10.1586/erv.12.126 Roadmap to developing a recombinant coronavirus S protein receptor-binding domain vaccine for severe acute respiratory syndrome.

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5	Tc bovine human IgG immunoglobulins against MERS-CoV (Luke 2016)	No vaccine, passive Ig	Two experimental MERS-CoV vaccines were used to vaccinate two groups of transchromosomic (Tc) bovines that were genetically modified to produce large quantities of fully human polyclonal immunoglobulin G (IgG) antibodies. 2 purified Tc bovine human IgG immunoglobulins (Tc hIgG), SAB-300 (produced after Jordan strain vaccination) and SAB-301 (produced after Al-Hasa strain vaccination), also had high ELISA and neutralizing antibody titers without antibody-dependent enhancement in vitro. SAB-301 was selected for in vivo and preclinical studies. Passive immunotherapy, but antiviral effect seen when given 24 or 48h post-MERS infection.	No info	www.ScienceTranslationalMedicine.org 17 February 2016 Human polyclonal immunoglobulin G from transchromosomic bovines inhibits MERS-CoV in vivo
6	Inactivated SARS-CoV Z-1 vaccine (Luo 2018)	NHP macaques	Higher concentrations of anti-sera against SARS-CoV neutralized the SARS-CoV infection, while highly diluted anti-sera significantly increased the SARS-CoV infection and triggered ADE in macaques; effects have been reported by others. The immunogenicity and efficacy of these experimental vaccines have been evaluated in animal models such as mice, ferrets, hamsters, and non-human primates. From Wuhan Center for Virology	No groups had obvious disease symptoms, virus titers and rate of PCR+ were lower in lungs of immunized but interstitial pnx seen in vaccinated and control Rhesus macaques with **no enhanced disease**.	https://doi.org/10.1007/s12250-018-0009-2 Evaluation of Antibody-Dependent Enhancement of SARS-CoV Infection in Rhesus Macaques Immunized with an Inactivated SARS-CoV Vaccine

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7	Multiple animal models & vaccines for SARS-CoV, review (Roberts 2008)	Mouse Hamster Ferrets Macaques	List of vaccines as of 2008; material is dated. Several inbred mouse species (BALB/c, C57BL/6 (B6), 129S) have been shown to support SARS-CoV replication and to demonstrate pneumonitis (129S) and clinical signs of SARS disease (aged BALB/c). Golden Syrian hamster (strain LVG}, is an excellent model for SARS-CoV infection because viral replication is accompanied by pathological changes in the lungs including pneumonitis and consolidation. Ferrets support SARS-CoV replication and develop multifocal pulmonary lesions involving 5–10% of the surface area of the lung. Various strains of SARS-CoV have been evaluated in rhesus macaques, cynomolgus macaques, common marmosets, African green monkeys, squirrel monkeys and mustached tamarins (latter 2 not infected).	Evidence of disease enhancement has not been seen in any of the studies where appreciable levels of neutralizing antibodies were achieved following vaccination (See references in Table 4). Furthermore, enhanced disease has not been reported in respiratory tissues or in GI tissues, which are the primary sites of viral replication in SARS-CoV infection. In a single set of experiments (Weingartl et al., 2004a), ferrets were immunized with MVA-SARS-S via IP and SC routes with 10^8 pfu of vaccine per ferret at day 0, boosted with the same regimen at day 14, and challenged intranasally at day 28. MVA-SARS-S vaccinated ferrets demonstrated low levels of neutralizing antibodies to SARS-CoV one week after the booster immunization (i.e. day 21; titer 1:40 or less), but not detectable at day 28 (<1:20), prior to challenge and no significant difference was observed in the level of virus	doi:10.1016/j.virusres.2007.03.025. Animal Models and Vaccines for SARS-CoV Infection. Virus Res. 2008 April ; 133(1): 20–32.

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				detected in pharyngeal swabs from animals vaccinated with MVA-SARS-S and control animals following challenge with SARS-CoV. Foci of hepatic necrosis were observed in MVA-SARS-S-vaccinated animals and to a lesser extent, in animals immunized with the MVA vector alone or PBS. It is unclear why the MVA-SARS-S vaccine was so poorly immunogenic (indicated by low level and transient detection of neutralizing antibodies) in ferrets since a similar vaccine was immunogenic and efficacious in mice and NHPs. It is also unclear why a memory antibody response was observed in MVA-SARS-S – immunized animals but was unable to neutralize virus or clear virus from these ferrets any faster than virus was cleared from mock-immunized ferrets. It is difficult to interpret the findings of hepatitis in ferrets and to determine if these findings have any relevance to	

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
				the possibility of disease enhancement in SARS-vaccinated animals. Although unconfirmed, it may be possible that hepatic lesions observed in this study occur through cell-mediated mechanisms similar to that observed in the lungs in RSV infection following the use of a formalin inactivated vaccine. The finding of hepatitis following use of this MVA-vectored vaccine in ferrets merits further evaluation.	
8	b-Propiolactone Inactivated Whole Virus SARS-CoV Vaccine +/- AS01b or AS03a adjuvant (Roberts 2010)	Hamster	AS01B-adjuvanted vaccine was slightly more immunogenic than the AS03A-adjuvanted vaccine in hamster model. Although antibody titers had declined in all groups 18 wk after the second dose, the vaccinated hamsters were still partially protected from wild-type virus challenge. Vaccine with adjuvant provided better protection than non-adjuvanted WI-SARS vaccine at this later time point.	Enhanced disease was not observed in the lungs or liver of hamsters following SARS-CoV challenge, regardless of the level of serum neutralizing antibodies.	VIRAL IMMUNOLOGY Volume 23, Number 5, 2010, Pp. 509–519 DOI: 10.1089/vim.2010.0028 Immunogenicity and Protective Efficacy in Mice and Hamsters of ab-Propiolactone Inactivated Whole Virus SARS-CoV Vaccine

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9	No vaccine, FIPV (Takano 2008)	Cats	Feline Infectious Peritonitis Virus model that suggests that re-infection with the same serotype induces ADE in cats infected with FIPV.	Inoculation of pathogen-free cats using FIPV serotype I enhanced the onset of FIP in cats passively immunized with FIPV serotype I-specific antibodies but not in those passively immunized with antibodies to FIPV serotype II.	J. Vet. Med. Sci. 70(12): 1315–1321, 2008 PMID:19122397 DOI: 10.1292/jvms.70.1315 Antibody-Dependent Enhancement Occurs Upon Re-Infection with the Identical Serotype Virus in Feline Infectious Peritonitis Virus Infection
10	VLP vaccine, 2 whole virus vaccines and an rDNA-produced S protein +/- alum (Tseng 2012)	Mouse (BALB/c, C57BL/6) Hamsters NHP	All 4 vaccines induced serum neutralizing antibody with increasing dosages and/or alum significantly increasing responses in BALB/c and C57BL/6 mice. Significant reductions of SARS-CoV two days after challenge were seen for all vaccines and prior live SARS-CoV. All mice exhibited histopathologic changes in lungs two days after challenge including all animals vaccinated (Balb/C and C57BL/6) or given live virus, influenza vaccine, or PBS suggesting infection occurred in all. Histopathology seen in animals given one of the SARS-CoV vaccines was uniformly a Th2-type immunopathology with prominent eosinophil infiltration, confirmed with special eosinophil stains. The pathologic changes seen in all control groups lacked the eosinophil prominence.	Prior occurrence in the initial preclinical trial of an immunopathogenic-type lung disease among ferrets and Cynomolgus monkeys given a whole virus vaccine adjuvanted with alum and challenged with infectious SARS-CoV. Th2-type immunopathology was seen after challenge of all vaccinated animals when evaluation for immunopathology was reported except the study in hamsters with a GSK whole virus vaccine.	PLoS One. 2012;7(4):e35421. doi: 10.1371/journal.pone.0035421. Epub 2012 Apr 20. Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus.

<table>
<tr><th>#</th><th>Vaccine(s) (1st Author Yr Published)</th><th>Animal Model</th><th>Findings</th><th>Enhanced Disease on Challenge Post-vaccination?</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>All vaccines containing S protein induced protection against infection while studies with VEE and vaccinia vector containing the N protein gene only did not.

Table 2. Summary of Reported Protection and Immunopathology in Animal Model Studies with SARS Coronavirus Vaccines.

<table>
<tr><th>Animal Model</th><th>Vaccine[1]</th><th>Protection[2]</th><th>Immunopathology[3]</th></tr>
<tr><td>Mice</td><td>Whole virus[tr]</td><td></td><td></td></tr>
<tr><td></td><td>w alum</td><td>Yes</td><td>Yes</td></tr>
<tr><td></td><td>Whole virus[25,tr]</td><td></td><td></td></tr>
<tr><td></td><td>w alum</td><td>Yes</td><td>Yes</td></tr>
<tr><td></td><td>wo alum</td><td>Yes</td><td>Yes</td></tr>
<tr><td></td><td>VLP[17,tr]</td><td></td><td></td></tr>
<tr><td></td><td>w alum</td><td>Yes</td><td>Yes</td></tr>
<tr><td></td><td>wo alum</td><td>Yes</td><td>Yes</td></tr>
<tr><td></td><td>S Protein[tr]</td><td></td><td></td></tr>
<tr><td></td><td>w alum</td><td>Yes</td><td>Yes</td></tr>
<tr><td></td><td>wo alum</td><td>Yes</td><td>Yes</td></tr>
<tr><td></td><td>VEE Vector[15]</td><td></td><td></td></tr>
<tr><td></td><td>for N protein</td><td>No</td><td>Yes</td></tr>
<tr><td></td><td>for S protein</td><td>Yes</td><td>No</td></tr>
<tr><td></td><td>Vaccinia vector[18]</td><td></td><td></td></tr>
<tr><td></td><td>for N protein</td><td>No</td><td>Yes</td></tr>
<tr><td></td><td>for S protein</td><td>Yes</td><td>?No</td></tr>
<tr><td>Ferrets</td><td>Whole virus[11]</td><td></td><td></td></tr>
<tr><td></td><td>w alum</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Nonhuman Primate[4]</td><td>Whole virus[11]</td><td></td><td></td></tr>
<tr><td></td><td>w alum</td><td>Yes</td><td>Yes</td></tr>
</table></td><td>Thus, inactivated whole virus vaccines whether inactivated with formalin or beta propiolactone and whether given with or without alum adjuvant exhibited a Th2-type immunopathologic in lungs after challenge.
2 reports attributed the immunopathology to presence of the N protein in the vaccine; however, we found the same immunopathologic reaction in animals given S protein vaccine only, although it appeared to be of lesser intensity.
A Th2-type immunopathologic reaction on challenge of vaccinated animals has occurred in 3/4 animal models (not in hamsters) including 2 different inbred mouse strains with 4 different types of SARS-CoV vaccines, with and without alum adjuvant“</td><td></td></tr>
</table>

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			Hamsters Whole virus[22] w ASO1 Yes No [1]Reference for each indicated; tr = this report; w = with, wo = without. [2]Protection against infection (reduced lung virus after challenge). [3]Th2-type immunopathology as indicated by cellular infiltrates with prominence of eosinophils. [4]Cynomolgus monkeys. doi:10.1371/journal.pone.0035421.t002		
11	NO VACCINE (Yip 2016)	In vitro	Description of enhanced disease in SARS infection. Anti-SARS-CoV spike antibodies promote infection of primary human immune cells by SARS-CoV.	The antibody-dependent enhancement (ADE) infection pathway grants SARS-CoV an opportunity to infect primary human macrophages, but it does not sustain productive viral replication in the infected cells. ADE of SARS-CoV infection does not alter proinflammatory gene expression profile of primary human macrophages. Infectivity of SARS-CoV does not rely solely on the potency of target cells to bind – via Fcγ receptor II (CD32) - infectious immune complexes, but depends on the properties of the intracellular domain of the FcγRII.	Hong Kong Med J 2016;22(Suppl 4): S25-31. PMID:27390007 Antibody-dependent enhancement of SARS coronavirus infection and its role in the pathogenesis of SARS.

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12	Adjuvanted (alum or VAP) and an unadjuvanted double inactivated SARS-CoV (DIV) vaccine (Bolles 2011)	Mouse (BALB/c and BALB/cBy)	DIV vaccine performed poorly in young BALB/c and BALB/cBy mice challenged with lethal homologous or heterologous strains. In contrast, DIV vaccines (both adjuvanted and unadjuvanted) performed poorly in aged-animal models. In young and aged animals, the presence of alum in the DIV vaccine formula significantly improved the induction of SARS-CoV neutralizing antibody: from moderate to high levels in young animals and from unmeasurable to moderate levels in aged animals.	Aged mice displayed increased eosinophilic immune pathology in the lungs and were not protected against significant virus replication.	J Virol. 2011 Dec;85(23):12201-15. doi: 10.1128/JVI.06048-11. Epub 2011 Sep 21. A double-inactivated severe acute respiratory syndrome coronavirus vaccine provides incomplete protection in mice and induces increased eosinophilic proinflammatory pulmonary response upon challenge.
13	Radiation inactivated MERS-CoV vaccine+/- alum or MF59 (Agrawal 2016)	Mouse (hCD26/DPP4 transgenic mouse model containing the human DPP4 receptor for MERS)	Inactivated MERS-CoV vaccine appears to carry a hypersensitive-type lung pathology risk from MERS-CoV infection that is similar to that found with inactivated SARS-CoV vaccines from SARS-CoV infection. Results of studies with vector vaccines point to the nucleoprotein (N) protein as responsible for the immunopathological effects seen and indicate that the S protein might be free of the risk; however, rS protein induced the pathology. The implication of the current study is that application of an **inactivated MERS-CoV vaccine for prevention of MERS in humans may carry a risk for lung immunopathology if subsequently exposed to MERS-CoV.**"	Lung mononuclear infiltrates occurred in all groups after virus challenge but with increased infiltrates that contained eosinophils and increases in the eosinophil promoting IL-5 and IL-13 cytokines only in the vaccine groups.	Hum Vaccin Immunother. 2016 Sep;12(9):2351-6. doi: 10.1080/21645515.2016.1177688. Epub 2016 Jun 7. Immunization with inactivated Middle East Respiratory Syndrome coronavirus vaccine

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					leads to lung immunopathology on challenge with live virus.
14	Formalin-inactivated whole SARS virus vaccine (Darnell 2007)	Ferrets	The vaccine provided mild immune protection to the ferrets after challenge. No evidence of enhanced disease was observed in any of the ferrets. NOTE: Need to summarize which animal models show enhanced disease and which do not. *NB: See 10 for 2012 state of the art*.	No evidence of enhanced liver or lung disease induced by the inactivated whole-virus vaccine.	J Infect Dis. 2007 Nov 1;196(9):1329-38. Epub 2007 Sep 27. PMID:17922397 DOI: 10.1086/522431 Severe acute respiratory syndrome coronavirus infection in vaccinated ferrets.
15	Venezuelan equine encephalitis virus replicon particles (VRP)Recombinant SARS-CoV With Epidemic and Zoonotic Spike Variants (Deming 2006)	Mouse (female BALB/c young and old)	VRP-S, but not VRP-N vaccines provide complete short- and long-term protection against homologous strain challenge in young and senescent mice. To test VRP vaccine efficacy against a heterologous SARS-CoV, used phylogenetic analyses, synthetic biology, and reverse genetics to construct a chimeric virus (icGDO3-S) encoding a synthetic S glycoprotein gene of the most genetically divergent human strain, GDO3, which clusters among the zoonotic SARS-CoV. icGD03-S replicated efficiently in human airway epithelial cells and in the lungs of young and senescent mice, and was highly resistant to neutralization with antisera directed against the Urbani strain. Although VRP-S vaccines provided complete short-term protection against heterologous icGD03-S challenge in young mice, only limited protection was seen in vaccinated senescent animals.	VRP-N vaccines not only failed to protect from homologous or heterologous challenge, but resulted in enhanced immunopathology with eosinophilic infiltrates within the lungs of SARS-CoV–challenged mice. VRP-N–induced pathology presented at day 4, peaked around day 7, and persisted through day 14, and was likely mediated by cellular immune responses	PLoS Med. 2006 Dec;3(12):e525. PMID:17194199 PMCID: PMC1716185 DOI: 10.1371/journal.pmed.0030525 Vaccine efficacy in senescent mice challenged with recombinant SARS-CoV bearing epidemic and zoonotic spike variants.

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			VRP-S vaccines provided complete short-term protection against heterologous icGD03-S challenge in young mice, only limited protection was seen in vaccinated senescent animals.		
16	Adeno-Associated Virus Encoding Receptor-Binding Domain SARS Coronavirus Spike Protein (RBD-rAAV Vaccine) (Du 2008)	Mouse (BALB/c)	In this study, systemic, mucosal, and cellular immune responses and long-term protective immunity induced by RBD-rAAV were further characterized in a BALB/c mouse model, with comparison of the i.m. and intranasal (i.n.) routes of administration. With intranasal vaccination, higher titers of mucosal IgA and serum-neutralizing Ab were associated with lower viral load and less pulmonary pathological damage upon challenge.	No Ab-mediated disease enhancement effect was observed.	J Immunol. 2008 Jan 15;180(2):948-56. PMID:18178835 PMCID: PMC2603051 DOI: 10.4049/jimmunol.180.2.948 Intranasal vaccination of recombinant adeno-associated virus encoding receptor-binding domain of severe acute respiratory syndrome coronavirus (SARS-CoV) spike protein induces strong mucosal immune responses and provides long-term protection against SARS-CoV infection.
17	Nucleocapsid SARS vaccine (Yasui 2008)	Mouse (BALB/c)	SARS-CoV-infected BALB/c mice that were immunized intradermally with recombinant vaccinia virus (VV) that expressed either the SARS-CoV spike (S) protein (LC16m8rVV-S) or simultaneously all the structural proteins, including the	LC16mOrVV-N-immunized mice upon infection exhibited significant up-regulation of both Th1 (IFN-gamma, IL-2)	Yasui F, Kai C, Kitabatake M, Inoue S, Yoneda M, et al.

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			nucleocapsid (N), membrane (M), envelope (E), and S proteins (LC16m8rVV-NMES) 7-8 wk before intranasal SARS-CoV infection.	and Th2 (IL-4, IL-5) cytokines and down-regulation of anti-inflammatory cytokines (IL-10, TGF-beta), resulting in robust infiltration of neutrophils, eosinophils, and lymphocytes into the lung, as well as thickening of the alveolar epithelium. Immunization with SARS nucleocapsid antigen causes severe enhanced disease on challenge.	(2008) J Immunol 181: 6337–6348. PMID:18941225 DOI: 10.4049/jimmunol.181.9.6337 Prior immunization with severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV) nucleocapsid protein causes severe pneumonia in mice infected with SARS-CoV.
18	Recombinant native full-length S-protein trimer (triSpike) (Kam 2007)	Hamsters	SARS-CoV-specific serum and mucosal immunoglobulins were readily detected in immunized animals. Serum IgG blocked binding of the S-protein to the ACE2 receptor and neutralized SARS-CoV infection in vitro. Entry into human B cell lines occurred in a FcRII-dependent and ACE2-independent fashion indicating that ADE of virus entry is a novel cell entry mechanism of SARS-CoV. Results indicate that a recombinant trimeric S protein was able to elicit an efficacious protective immune response in vivo and warrant concern in the safety evaluation of a human vaccine against SARS-CoV.	Vaccinated hamsters showed no signs of enhanced lung pathology or hepatitis and viral load was undetectable or greatly reduced in lungs following challenge with SARS-CoV. Recombinant trimeric S protein was able to elicit a protective immune response in vivo but if the observation of enhanced entry into B cells in vitro can be shown to have an in vivo correlate, this would warrant concern in the safety	Vaccine 25 (2007) 729–740. PMID:17049691, DOI: 10.1016/j.vaccine.2006.08.011 Antibodies against trimeric S glycoprotein protect hamsters against SARS-CoV challenge despite their capacity to mediate FcRII-dependent

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				evaluation of a human vaccine against SARS-CoV.	entry into B cells in vitro
19	No vaccine (Luo 2007)	NHP (rhesus macaques)	Animal model described in rhesus macaques that correlates with human SARS.	NA	Acta virologica 51: 171 – 177, 2007 PMID:1807630 Intratracheal inoculation of severe acute respiratory syndrome coronavirus in monkeys macaca rhesus
20	b-propiolactone inactivated alum-containing purified vaccine, purified vaccine + unpurified vaccine for SARS (Qin 2006)	NHP (Cynomolgus macaques)	Purified inactivated SARS vaccine could induce high levels of neutralizing antibody, protect monkeys after a SARS-CoV challenge, and be administered safely in monkeys.	Under low levels of neutralizing antibody, no exacerbation of clinical symptoms was observed when the immunized monkeys were challenged with SARS-CoV	Vaccine 24 (2006) 1028–1034. PMID: 16388880, DOI: 10.1016/j.vaccine.2005.06.038 Immunogenicity and protective efficacy in monkeys of purified inactivated Vero-cell SARS vaccine
21	In vitro studies of ADE (Wang 2014)	In vitro	Observations of SARS-CoV using ADE to enhance the infectivity of a HL-CZ human promonocyte cell line. SARS-CoV is capable of replication in HL-CZ cells, and of displaying virus-induced cytopathic effects and increased levels of TNF-a, IL-4 and IL-6 two days post-infection. HL-CZ cells also expressed angiotensin converting enzyme 2 (ACE2, a SARS-CoV receptor) and higher levels of the FcgRII receptor.	Data suggest that antibodies against SARS-CoV spike proteins may trigger ADE effects. The data raise new questions regarding a potential SARS-CoV vaccine, while shedding light on	Biochem and Biophys Research Commun 451 (2014) 208–214 PMID:25073113 DOI: 10.1016/j.bbrc.2014.07.090

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			Higher concentrations of anti-sera against SARS-CoV neutralized SARS-CoV infection, while highly diluted anti-sera significantly increased SARS-CoV infection and induced higher levels of apoptosis. SARS-CoV ADE is primarily mediated by diluted antibodies against envelope spike proteins rather than nucleocapsid proteins. MoAbs against SARS-CoV spike proteins promoted SARS-CoV infection.	mechanisms involved in SARS pathogenesis.	Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins.
22	Different forms of SARS coronavirus (SARS-CoV) spike protein-based vaccines (Woo 2005)	Mouse	Prime//boost DNA with spike polypeptide boost regimen. No statistical significant difference was observed among the Th1/Th2 index among these six groups of mice with high IgG levels. Among all the combinations of vaccines examined, mice primed with SARS-CoV human codon usage optimized spike polypeptide DNA vaccines and boosted with S-peptide produced by E. coli generated the highest titer of neutralizing antibody against SARS-CoV. Useful for civet cat vaccine?	NA	Vaccine 23 (2005) 4959–4968. PMID: 15993989, DOI: 10.1016/j.vaccine.2005.05.023 SARS coronavirus spike polypeptide DNA vaccine priming with recombinant spike polypeptide from Escherichia coli as booster induces high titer of neutralizing antibody against SARS coronavirus.
23	In vitro studies re: SARS, no vaccine (Yip 2014)	In vitro	Used primary human immune cells to evaluate their susceptibility to infection by SARS-CoV in the presence of anti-Spike antibodies. Results demonstrate that, in presence of vaccine-elicited antiviral antibodies, SARS-CoV displays an altered tropism toward primary human immune cells, which do not express the conventional virus receptor and are otherwise refractory to the virus.	Anti-Spike immune serum increased infection of human monocyte-derived macrophages by replication-competent SARS-CoV as well as Spike-pseudotyped	Virology Journal 2014,11:82 PMID: 24885320, PMCID: PMC4018502, DOI: 10.1186/1743-422X-11-82

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				lentiviral particles (SARS-CoVpp). Macrophages infected with SARS-CoV did not support productive replication of the virus. Purified anti-viral IgGs were sufficient to enhance infection. Antibody-mediated infection was dependent on signaling-competent members of the human FcγRII family, which were shown to confer susceptibility to otherwise naïve ST486 cells. Only FcγRII with intact cytoplasmic signaling domains were competent to sustain ADE of SARS-CoVpp infection.	Antibody-dependent infection of human macrophages by severe acute respiratory syndrome coronavirus.
24	Formaldehyde-inactivated Vero cell vaccine for SARS (Zhou 2005)	NHP (rhesus monkeys)	The control animals who received PBS developed atypical SAR-CoV infection after viral challenge, according to clinical, virological and pathological findings. No systematic side effects in vaccinated animals post-immunization, even in at the high dose of 5000 mcg. The 50 mcg dosage of vaccine elicited SARS-CoV specific immune responses against viral infection as compared to the partial immunity elicited by 0.5 and 5 mcg doses. This inactivated vaccine can induce effective concomitant humoral and mucosal immunity against SARS-CoV infection, is safe in monkeys.	No clinical signs or CXR changes in immunized monkeys but PBS group had mild disease. No real ADE data.	Vaccine 23 (2005) 3202–3209, PMID: 15837221, DOI: 10.1016/j.vaccine.2004.11.075 Immunogenicity, safety, and protective efficacy of an inactivated SARS-associated

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
					coronavirus vaccine in rhesus monkeys
25	Multiple SARS vaccines, review (Enjuanes 2008)	Ferrets, Mouse, Hamsters, NHP	Comprehensive review of state of the art for SARS vaccines as of 2008	Administration into ferrets of MVA-based SARS-CoV S vaccine resulted in enhanced hepatitis on challenge which has not been reported in other studies with SARS-CoV in ferrets and was not reproduced by other groups. Antibodies directed against SARS-CoV were protective and did not enhance viral infectivity in the mouse or hamster models using inactivated SARS-CoV or immunization with recombinant adenovirus vectors expressing the S and N proteins of SARS-CoV. Side effects were not observed in other animal models that were challenged with SARS-CoV and no evidence of enhanced disease upon re-challenge was shown. Cynomolgus macaques immunized with different amounts of purified virus, +/- adjuvant, showed no side effects even in the presence of	Virus Res. 2008 April; 133(1): 45–62. doi:10.1016/j.virusres.2007.01.021. Vaccines to prevent severe acute respiratory syndrome coronavirus-induced disease.

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
				low titer neutralizing antibodies. No abnormalities were observed in major organs. Immunization of mice using either S protein or whole inactivated virus or of monkeys with whole inactivated SARS-CoV most frequently resulted in the absence of side effects after providing different types of SARS-CoV vaccines. In contrast, VEE virus expressing N protein failed to induce protection in either young or senescent animals and resulted in enhanced immunopathology following viral challenge. Co-expression of N protein in vaccine regimens which failed to simultaneously induce a strong neutralizing anti-S antibody response led to an increased number of lymphocytic and eosinophilic inflammatory infiltrates, which are also characteristic of the immune pathology observed with respiratory syncytial virus (RSV) infection following	

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
				vaccination with formalin inactivated RSV.	
26	Recombinant full-length Spike-protein trimers (Jaume 2011)	In vitro	We previously reported that a SARS-CoV vaccine candidate based on recombinant, full-length SARS-CoV Spike-protein trimers triggered infection of human B cell lines despite eliciting in vivo a neutralizing and protective immune response in rodents. Paper describes in vitro experiments re: mech of action for ADE using serum from immunized mice.	Anti-Spike immune serum, while inhibiting viral entry in a permissive cell line, potentiated infection of immune cells by SARS-CoV Spike-pseudotyped lentiviral particles, as well as replication-competent SARS coronavirus. Antibody-mediated infection was dependent on Fcg receptor II but did not use the endosomal/lysosomal pathway utilized by angiotensin I converting enzyme 2 (ACE2), the accepted receptor for SARS-CoV. ADE of SARS-CoV utilizes a novel cell entry mechanism into immune cells. Different SARS vaccine candidates elicit sera that differ in their capacity to induce ADE in immune cells despite their comparable potency to neutralize infection in ACE2-bearing cells.	J OF VIROLOGY, Oct. 2011, p. 10582–10597 Vol. 85, No. 20 0022-538X/11/$12.00 doi:10.1128/JVI.00671-11 Anti-Severe Acute Respiratory Syndrome Coronavirus Spike Antibodies Trigger Infection of Human Immune Cells via a pH- and Cysteine Protease-Independent FcgR Pathway.

<table>
<tr><th>#</th><th>Vaccine(s)
(1st Author Yr Published)</th><th>Animal Model</th><th>Findings</th><th>Enhanced Disease on Challenge Post-vaccination?</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>26</td><td>No vaccines, review of CoV immunopathogenisis

(Perlman 2005)</td><td colspan="2"><table>
<tr><th>Mechanism</th><th>Description</th><th>Coronavirus example</th><th>References</th></tr>
<tr><td>Inflammatory storm</td><td>Excessive host response to pathogen occurs, resulting in either increased severity of localized disease or systemic disease; excessive response might be non-specific or induced by specific viral proteins; and manifestations might also occur as part of the ‘normal’ immune response required for viral clearance</td><td>MHV, FIPV, SARS-CoV</td><td>7,8,40,59</td></tr>
<tr><td>Bystander activation</td><td>T cells that are not specific for the pathogen or any host protein that is expressed at the site of inflammation are nevertheless activated (possibly by cytokines), resulting in increased tissue damage</td><td>MHV</td><td>74,111</td></tr>
<tr><td>Molecular mimicry</td><td>Pathogen and host share B- or T-cell epitopes, resulting in an autoimmune reaction in the host tissue that expresses the protein</td><td>None</td><td>–</td></tr>
<tr><td>Epitope spreading</td><td>Ongoing inflammation leads to presentation of self-epitopes, resulting in an autoimmune reaction in the host tissue that expresses the protein</td><td>MHV</td><td>69</td></tr>
<tr><td>Antibody-dependent enhancement</td><td>Antibodies specific for cell-surface glycoproteins increase virus uptake by macrophages, through cell-surface Fc receptors, resulting in disease enhancement</td><td>FIPV, possibly SARS-CoV</td><td>40,99,105</td></tr>
</table></td><td>Perlman S, Dandekar AA (2005) Nature Rev Immunol 5: 917–927.32. DOI: 10.1038/nri1732

Immunopathogenesis of coronavirus infections: Implications for SARS.</td></tr>
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#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
		Fc receptor, receptor for immunoglobulin; FIPV, feline infectious peritonitis virus; MHV, murine hepatitis virus; SARS-CoV, severe- acute-respiratory-syndrome coronavirus. As discussed in this Review, studies of animals that are infected with other coronaviruses indicate that excessive and sometimes dysregulated responses by macrophages and other pro-inflammatory cells might be particularly important in the pathogenesis of disease that is caused by infection with these viruses.			
27	Coronavirus-like particles (VLPs) for SARS (Lokugamage 2008)	Mouse (BALB/c)	Studied efficacy of coronavirus-like particles (VLPs) for protecting mice against severe acute respiratory syndrome coronavirus (SCoV) infection. Coexpression of SCoV S protein and E, M and N proteins of mouse hepatitis virus in 293T or CHO cells. Balb/c mice inoculated with a mixture of chimeric VLPs and alum were protected from SCoV challenge. The same groups of mice had high levels of SCoV-specific neutralizing antibodies suggesting that SCoV-specific neutralizing antibodies are important for the suppression of viral replication within the lungs.	Not seen. Despite some differences in the cellular composition of inflammatory infiltrates, no overt lung pathology in the chimeric-VLP-treated mice compared to negative control mice.	Vaccine 26: 797–808. Lokugamage KG, Yoshikawa-Iwata N, Ito N, Watts DM, Wyde PR, et al. (2008) PMID:18191004 PMCID: PMC2267761 DOI: 10.1016/j.vaccine.2007.11.092 Chimeric coronavirus-like particles carrying severe acute respiratory syndrome coronavirus (SCov) S protein protect mice against challenge with SCoV.
28	DNA vector, inactivated SARS virus, recombinant adenoviral vector	Mouse (BALB/c)	Cellular and humoral immune responses elicited by different combinations of gene-based and inactivated viral particles with various adjuvants have been assessed in Balb/C mice. Optimal CD8 immunity induced by DNA priming and replication-defective adenoviral vector boosting.	NA	J Virol 2005;79:13915–13923. [PubMed: 16254327] Kong WP, Xu L, Stadler K,

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
	encoding S with MF59 or CpG adjuvants (Kong 2005)		Humoral immune response was enhanced most effectively through the use of inactivated virus with adjuvants, either MF59 or alum, and was associated with stimulation of the CD4 but not the CD8 response. Inactivated SARS virus with MF59 enhanced the CD4 and antibody response even after gene-based vaccination. The ability to boost gene-based vaccines with the adjuvanted inactivated virus shows clear enhancement of the CD4 and antibody responses. The CD8 responses are not similarly enhanced after such a boost. In contrast, DNA priming followed by rAd boosting with vectors encoding S allow induction of a strong CD8 response.		Ulmer JB, Abrignani S, Rappuoli R, Nabel GJ. PMID:16254327 PMCID: PMC1280202 DOI: 10.1128/JVI.79.22.13915-13923.2005 Modulation of the immune response to the severe acute respiratory syndrome spike glycoprotein by gene-based and inactivated virus immunization.
29	Spike (S) protein or inactivated whole MERS-CoV (IV) with a combined adjuvant (alum+CpG) (Deng 2018)	Mouse (transduced with Ad5-hDPP4 after final immuniza-tion)	In mice, similar levels of the anti-S protein IgG response and neutralizing activity were induced by both the S protein and IV vaccines. Immune responses against three other structural proteins, the envelope (E), membrane (M), and nucleocapsid (N) proteins, were also detected in sera of mice that received IV. No antigen-specific T-cell immunity was detected. Mice were transduced with Ad5-hDPP4 after the final immunization and were then challenged with MERS-CoV. Mice immunized with the S protein or IV showed slightly lower pathological damage in the lung, reduced antigen expression and lung virus titers. Mice that received IV formulations also showed increased protective immunity (almost no live virus was isolated from the lung).	Not seen as lung pathology scored as mod for both vaccines vs. severe for adj controls. Work differs from that of Tseng et al. in preparation of IV (inactivated with 0.4% formaldehyde vs. gamma [γ] irradiation), adjuvant formulation (Al+CpG vs. Al or MF59), and animal model (Ad5-hDPP4 transduced mice vs. hCD26/DPP4 transgenic mice).	Emerg Microbes Infect. 2018 Apr 4;7(1):60. doi: 10.1038/s41426-018-0056-7. Enhanced protection in mice induced by immunization with inactivated whole viruses compared to spike protein of middle east respiratory syndrome coronavir us.

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
30	Recombinant S377–588-Fc from MERS-CoV +/- several adjuvants (Zhang 2016)	Mouse (BALB/c)	Residues 377–588 of MERS-CoV spike (S) protein receptor-binding domain (RBD) is a very promising MERS subunit vaccine candidate. Compared several adjuvants, including Freund's adjuvant, aluminum, Monophosphoryl lipid A, Montanide ISA51 and MF59 with regard to their capacity to enhance the immunogenicity of this subunit S377–588-Fc vaccine. S377–588-Fc alone induced readily detectable neutralizing antibody and T-cell responses in immunized mice. MF59 is the most potent adjuvant as judged by superior ability to induce the highest titers of IgG, IgG1 and IgG2a subtypes, and neutralizing antibodies. Addition of MF59 also increased protection against MERS-CoV infection in BALB/c mice.	Not seen; MERS-CoV was detected in lungs of mice immunized with S377–588-Fc + MF59 3 and 5 days, post-infection, while high titers found in mice inoculated with PBS + MF59 adjuvant, suggesting that in the presence of MF59, MERS-CoV RBD is highly effective in protecting mice from MERS-CoV challenge. Other formulations not tested.	Cell Mol Immunol. 2016 Mar;13(2):180-90. doi: 10.1038/cmi.2015.03. Epub 2015 Feb 2. Identification of an ideal adjuvant for receptor-binding domain-based subunit vaccines against Middle East respiratory syndrome coronavirus.
31	Several attenuated mutants (rSARS-CoV-MA15-E*) (Regla-Nava 2015)	Mouse (BALB/c)	To identify E protein regions and host responses that contribute to rSARS-CoV-MA15-ΔE attenuation, mutants (rSARS-CoV-MA15-E*) containing point mutations or deletions in the amino-terminal or the carboxy-terminal regions of the envelope (E) protein were generated. Small deletions and modifications within the E protein led to virus attenuation, manifested by minimal lung injury, limited neutrophil influx to the lungs, reduced expression of proinflammatory cytokines, increased anti-inflammatory cytokine levels, and enhanced $CD4^+$ and $CD8^+$ T cell counts *in vivo*, suggesting that these phenomena contribute to virus attenuation. The attenuated mutants fully protected mice from challenge. The major problems of using live attenuated vaccines are the possibility that the viruses may revert to virulence so they are introducing additional attenuating mutations into the Nsp1 protein to generate a safer vaccine candidate.	No enhancement seen clinically. Challenge with virulent SARS-CoV-MA15, was studied in BALB/c mice. All the nonimmunized mice lost weight and died by day 7 after rSARS-CoV-MA15 challenge. Vaccination with the attenuated mutant viruses completely protected mice from the lethal dose of SARS-CoV-MA15, as they showed no weight loss and all survived (no path).	J Virol. 2015 Apr;89(7):3870-87. doi: 10.1128/JVI.03566-14. Epub 2015 Jan 21. Severe acute respiratory syndrome coronaviruses with mutations in the E protein are attenuated and promising vaccine candidates.

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
32	In vitro studies with moAb MERS (Wan 2019)	In vitro	Investigated how a neutralizing monoclonal antibody (mAb), which targets the receptor-binding domain (RBD) of MERS coronavirus spike, mediates viral entry. Results showed that mAb binds to the virus-surface spike, allowing it to undergo conformational changes and become prone to proteolytic activation. mAb binds to cell-surface IgG Fc receptor, guiding viral entry through canonical viral-receptor-dependent pathways. Antibody/Fc-receptor complex functionally mimics viral receptor in mediating viral entry.	NA but couldn't access full article so based on abstract review	J Virol. 2019 Dec 11. pii: JVI.02015-19. doi: 10.1128/JVI.02015-19. [Epub ahead of print] Molecular mechanism for antibody-dependent enhancement of coronavirus entry
33	Editorial MERS, review (Li 2019)	Camels. Alpacas, NHP, Rabbit, Mouse	Whereas SARS-CoV recognizes angiotensin-converting enzyme 2 (ACE2) as a cellular receptor [9,10], MERS-CoV uses dipeptidyl peptidase 4 (DPP4) to enter target cells [11,12]. Dromedary camels, alpacas, and non-human primates are susceptible to MERS-CoV infection [21–23]; however, the virus does not infect small animals such as mice, hamsters, and ferrets [24–26]. MERS-CoV infects rabbits without causing symptoms; they also analyze the route of MERS-CoV transmission in rabbits [30]. Fan and colleagues report the development of an hDPP4-expressing mouse model through inserting hDPP4 gene into a constitutive and ubiquitous gene expression locus using CRISPR/Cas9 technology. This mouse model is susceptible to MERS-CoV infection [31]. Efficacy of a MERS-CoV S1 subunit vaccine aided by adjuvants; with reduced and delayed viral shedding in dromedary camels as well as the complete protection of alpacas from MERS-CoV infection [38]. This and other studies demonstrate that the protective efficacy of		Viruses. 2019 Jul 19;11(7). pii: E663. doi: 10.3390/v11070663 MERS Coronavirus: An Emerging Zoonotic Virus

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
			MERS vaccines positively correlates with neutralizing antibody titers in serum [38,39]. Veit and colleagues report that a MERS-CoV N protein-based vaccine, which is delivered through a modified Vaccinia virus, induces CD8+ T cell responses in a mouse model; they further identify a MERS-CoV N protein-specific CD8+ T cell epitope on the vaccine [40].		
34	Review of multiple MERS-CoV spike vaccines (Zhou 2018)	Mouse Camel NHP	Viral vector-, DNA-, nanoparticle-, virus-like particle (VLP)-, and S-trimer protein-based subunit vaccines [30,31,56–60]. Many of the reported full-length S-based vaccines have been tested in suitable animal models, and they demonstrated efficacy against MERS-CoV infection [31,53,57,61,62]. A full-length S-based simian adenovirus vector vaccine (ChAdOx1) and a DNA vaccine (GLS-5300), are scheduled for clinical trials (Phase I). Viral vector-based vaccines encoding full-length S protein of MERS-CoV among which human or simian Ad, modified Vaccinia Ankara (MVA), measles virus (MV), and vesicular stomatitis virus (VSV) can be employed as the vaccine vehicles. For example, MERS-CoV S/RBD-specific systemic, mucosal, and/or cellular immune responses, as well as neutralizing antibodies against pseudotyped and live MERS-CoV, are induced in mice after immunizing them with human Ad5-based and Ad41-based or simian adenovirus vector (ChAdOx1)-based MERS-CoV full-length S-encoding vaccines [56,61,65,66], protecting hDPP4-Tg mice against MERS-CoV infection [61]. MERS-CoV S-specific systemic and mucosal antibody responses and T cell responses, particularly neutralizing antibodies, are elicited in mice and/or camels immunized with MERS-CoV full-length S-expressing MVA vaccines, protecting Ad5/hDPP4-transduced mice and dromedary camels against MERS-CoV infection [31,62,67].	By optimizing and comparing five RBD fragments with different lengths, a RBD fragment containing residues 377–588 of MERS-CoV S protein is identified to induce the highest titer of antibody responses and neutralizing antibodies in immunized mice and rabbits with the capability of protecting Ad5/hDPP4 and hDPP4-Tg mice from MERS-CoV challenge with no evidence of immunological toxicity or eosinophilic immune enhancement [32,33,75,76,81]. At present, no vaccines are reported solely based on the MERS-CoV S2 subunit, potentially because of its low immunogenicity and inability to induce strong neutralizing antibodies.	Expert Rev Vaccines. 2018 Aug;17(8):677-686. doi: 10.1080/14760584.2018.1506702. Epub 2018 Aug 9. Prospects for a MERS-CoV spike vaccine.

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
			MERS-CoV S-specific immune responses and neutralizing antibodies are significantly improved by the Ad (ChAdOx1)-S vaccine priming and MVA-S vaccine boosting approach [65]. In addition, a full-length S-encoding MV vaccine induces MERS-CoV S-specific antibody and T cell responses, as well as MERS-CoV neutralizing antibodies, protecting Ad5/hDPP4-transduced mice from MERS-CoV challenge [68]. VSV-based MERS-CoV full-length S vaccine is shown to elicit MERS-CoV neutralizing antibodies and T cell responses in mice and/or NHPs [69]. Other types of MERS-CoV S-based vaccines, including those based on DNA, S-trimer protein, nanoparticle, and VLP, have shown immunogenicity and/or protective efficacy against MERS-CoV infection in mouse, camel, and NHP models [30,53,57–59]. Depending on antigen doses, injection doses, or immunization routes, MERS-CoV S/RBD-specific antibody and cellular immune responses and MERS-CoV neutralizing antibody titers induced by viral vectored full-length S vaccines might vary [61,62], while the titer of neutralizing antibodies elicited by other vaccine types, such as nanoparticle vaccines, could be significantly affected by adjuvants, not by antigen doses [53,60]. In addition to inducing MERS-CoV-specific immune responses and neutralizing antibodies, viral vector-based full-length MERS-CoV S vaccines generally elicit anti-vector immune responses and/or neutralizing antibodies [31,62,65,68], a phenomenon that can be easily eliminated by S-based other vaccine types, such as DNA, S-trimer protein, nanoparticle, and VLP. As a short fragment inside the S1 subunit of MERS-CoV S protein, the RBD is applied as a key target for developing MERS vaccines in the categories of VLP and subunit vaccines, and their immunogenicity and efficacy have been tested in mouse, rabbits, and NHP models	MERS-CoV S1 subunit, which is much longer than the RBD, also contains some non-neutralizing immunodominant epitopes. Such immunodominant epitope in SARS-CoV S1 is shown to elicit epitope sequence-dependent enhancement of viral infection [89]. Therefore, evaluation of the safety and potential immunopathological consequences is essential for full-length S and S1-based MERS vaccines before moving them to large-scale development and beginning clinical trials. RBD does not contain non-neutralizing epitopes that may cause harmful immune responses, and RBD-based vaccines do not show immunological toxicity and immunopathological effects in the animals tested [81]. Viral vectored vaccines, such as those based on Ad, against other viruses, including HIV, may induce a rapid memory immune response against the vector, enhance virus	

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
			Mammalian cell-expressed recombinant RBD protein containing residues 377–662 of MERS-CoV S induces robust humoral systemic and mucosal immune responses and neutralizing antibodies in immunized mice [32,78]. Studies have also shown that residues 358–588 and 367–606 of MERS-CoV RBD expressed in mammalian and insect cells, respectively, elicit RBD-specific antibody or cellular immune responses and neutralizing antibodies in mice and/or rabbits [79,80]. Immunogenicity of MERS-CoV RBD-based subunit vaccines is not significantly affected by antigen dosage, but by injection doses and vaccination intervals. MERS-CoV RBD-elicited immune responses and neutralizing antibodies are significantly improved in the presence of suitable adjuvants, such as MF59, or fusion with appropriate immunopotentiators, such as Fc tag [32]. Like SARS-CoV RBD-based vaccines that induce high titers of cross-neutralizing antibodies against divergent strains of human and animal SARS-CoV [91], MERS-CoV RBD-based vaccines also elicit broad-spectrum neutralizing antibodies and cross-protective immunity against infections of divergent MERS-CoV strains from humans, camels, and antibody escape mutants [74].	infection, or elicit limited efficacy in immunized hosts, resulting in early halting of clinical trials [93–95]. Thus, in addition to investigating immunogenicity and protection of viral-vectored MERS-CoV S candidate vaccines against MERS-CoV infection, careful design and selection of suitable viral vectors, comprehensive investigation of the possibility of anti-vector immunity in preventing MERS-CoV-specific immune responses, as well as extensive evaluation of their safety and potential toxicity, are needed before moving such vaccines forward for trials in humans. Overall, in order to further improve immunogenicity and efficacy, S-based MERS vaccines can be used alone or combined with other types of S or non-S vaccines with complementary effects by priming-boosting vaccination approaches, or conjugating with different adjuvants, and optimizing for doses, routes,	

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
				or intervals. Such vaccines should be tested in different animal models, including large animal models, such as NHPs and/or camels, to confirm immunogenicity, efficacy, toxicity, and immunopathology before processing to human clinical trials.	
35	Review of host factors MERS (Widagdo 2019)	Camel	Review of the role of DPP4 and other host factors in MERS-CoV transmission and pathogenesis—such as sialic acids, host proteases, and interferons. The dromedary camel is the only animal species that has been reported to transmit this virus to humans [13,14,15,16]. MERS-CoV infection in these animals merely causes mild upper respiratory tract infection [17,18], but seroepidemiological studies showed that this virus has been circulating in dromedary camels for decades. MERS-CoV infection is mediated by the binding of S1 protein to the β-propeller domain of DPP4 [28,29,30,31]. There are 11 critical residues within the β-propeller domain that directly interact with the S1 protein [29,30,31]. These residues are quite conserved in camelids, primates, and rabbits—species shown to be susceptible to MERS-CoV [17,31,32,33]. In contrast, ferrets, rats, and mice resist MERS-CoV infection due to differences in some critical DPP4 residues [31,34,35,36]. In humans, DPP4 is absent in the nasal epithelium but present in the lower respiratory tract epithelium, mainly in type II pneumocytes [69,70]. In contrast, DPP4 is expressed in the nasal epithelium of dromedary camels [69]. This difference in DPP4	No info	Viruses. 2019 Mar; 11(3): 280. Published online 2019 Mar19 PMCID: PMC6466079, PMID: 30893947 doi: 10.3390/v11030280 Host Determinants of MERS-CoV Transmission and Pathogenesis

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
			localization between humans and dromedary camels therefore explains MERS-CoV tropism in these two species. Two risk factors, i.e., smoking and chronic obstructive pulmonary disease (COPD), have been shown to upregulate DPP4 expression in the lungs.		
36	Review of MERS vaccine candidates (Schindewolf 2019)	NHP (rhesus macaques) Mouse	Studies of recovered SARS-CoV patients show that antibodies generated against the receptor binding domain (RBD) are both long-lasting (>3 years) and neutralizing [48]. RBD proteins encoding sequences from different strains of MERS-CoV have been shown to induce cross-neutralizing antibodies against divergent human and camel MERS-CoV strains as well as monoclonal antibody (mAb) escape mutants, confirming the promise of the RBD as a valid vaccine target. Vaccines targeting the N-terminal domain of S1 (NTD) offer a novel target. pVax1™ is a proprietary, optimized plasmid vaccine vector that has been developed as a MERS-CoV vaccine by encoding a consensus MERS-CoV S glycoprotein containing codon and other proprietary optimizations, as well as an IgE leader sequence to promote expression and mRNA export [71]. Intramuscular administration of this construct with electroporation induced antibodies with cross-MERS-CoV-strain neutralization and antigen-specific, polyfunctional T cell responses in rhesus macaques (completed Ph1). A vaccine regimen consisting of intramuscular administration of MERS-CoV strain England1 full-length S encoded on pVRC8400, with electroporation, and an $AlPO_4$-adjuvanted S1 protein booster, induced NAb in rhesus macaques up to 10 weeks following booster [74]. Multiple plasmid vaccine vectors encoding either full-length S or the S1 domain induce adaptive immunity and protect against MERS-CoV challenge.	Purified and adjuvanted with AddaVax™ (MF59-like), RBD protein vaccine was protective when administered IM to transgenic mice expressing human DPP4 (hDPP4), with no evidence of immunological toxicity or eosinophilic immune enhancement. While ADE has not been demonstrated with full length S from MERS-CoV, further studies must consider this as a potential issue. pVax1™ humoral and cell-mediated immune responses correlated with minimal lung pathology and reduced lung viral loads upon MERS-CoV challenge. Full-length S encoded on pVRC8400, with electroporation, and $AlPO_4$-adjuvanted S1 protein booster resulted in lower lung pathology upon challenge with	Viruses. 2019 Jan 17;11(1). pii: E74. doi: 10.3390/v11010074. Middle East Respiratory Syndrome Vaccine Candidates: Cautious Optimism.

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
			Venezuelan equine encephalitis (VEE) virus replicon particles (VRPs), an alphavirus-based platform that replaces the VEE structural genes with a foreign transgene, has been shown to induce strong humoral and cellular immune responses [80,81]. A VRP encoding MERS-CoV S elicited NAb in both young and aged mice [38]. An N protein-expressing VRP protected adenovirally hDPP4-transduced mice from MERS-CoV challenge in a CD4+ T cell- and IFN-γ-dependent manner [82]. Modified vaccinia virus Ankara (MVA) [83,84] has been developed to encode full-length MERS-CoV S, induced NAb and CD8+ T cell responses in mice [85], and also protected against MERS-CoV-induced histopathology in adenovirally hDPP4-transduced mice before challenge [86]. (Ph1 underway) Ad5-vectored full-length S and S1 vaccines have been developed [93]. These elicited antigen-specific IgG and NAb when administered intramuscularly to mice with subsequent intranasal boosting. Immunizing with Ad5-vectored S followed by boosting with S nanoparticles induced S-specific IgG, NAb, and both T_h1 and T_h2 cell-mediated responses in mice, and also protected adenovirally hDPP4-transduced mice from MERS-CoV challenge. To circumvent the seroprevalence of circulating human adenoviruses, chimpanzee adenoviruses have also been developed as viral vaccine vectors [97] and have entered clinical trials [98]. ChAdOx1-MERS-CoV S vaccine protected against lethal challenge in a transgenic hDPP4 mouse model [102] A full-length or soluble form of S encoded in measles vaccine strain MV_{vac2} induced NAb, proliferation of T cells, S-specific IFN-γ production, and cytotoxic activity [104]. The vaccine also protected against MERS-CoV challenge in adenovirally hDPP4-transduced mice that were transgenic for a measles virus receptor.	the MERS-CoV strain JordanN3. Eosinophil-related lung pathology was observed for a SARS-CoV vaccine doubly inactivated with both formalin and UV irradiation [115]. This response was particularly notable in aged mice versus young mice, and following heterologous versus homologous challenge. Similarly, immunization with a gamma-irradiated MERS-CoV vaccine adjuvanted with either alum or MF59 elicited NAb and reduced viral titer upon challenge in hDPP4-transgenic mice, but induced eosinophil-related lung pathology in vaccinated mice after challenge [116]. Formalin-inactivated MERS-CoV adjuvanted with alum and oligodeoxynucleotides containing unmethylated CpG motifs was shown to elicit levels of NAb on par with those elicited by an S glycoprotein-only vaccine [117]. Moreover, the vaccine offered better protection than	

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
			An NVD vector expressing MERS-CoV S was shown to induce long-lasting (up 14 weeks post-immunization) NAb titers in camels [107]. β-propiolactone-inactivated dual rabies/MERS vaccine has been proposed which incorporates the MERS-CoV S1 domain fused to rabies virus G protein on the RABV virion [111]. This vaccine elicited S-specific IgG and NAb and fully protected adenovirally hDPP4-transduced mice from MERS-CoV challenge. A baculovirus VLP containing S as well as MERS-CoV envelope and matrix proteins elicited RBD-specific IgG and IFN-γ responses in rhesus macaques [113]. A subsequent baculovirus VLP vaccine was developed that focused only on a fusion of the RBD from S and the immunogenic VP2 protein of canine parvovirus. This vaccine induced RBD-specific IgG, NAb, and cell-mediated responses including IFN-γ, IL-2, and IL-4 production in mice, and also activated dendritic cells in inguinal lymph nodes [114].	S alone based on reduction of lung viral titer in adenovirally hDPP4-transduced mice after MERS-CoV challenge. Remarkably, eosinophil-mediated vaccine-related pathology was not observed in this animal model. It has also been shown that including Toll-like receptor agonists in a UV-inactivated SARS-CoV vaccine reduced T_h2-associated pathology in lungs after challenge [118].	
37	Review SARS to MERS (Song 2019)	Mouse Hamster Ferrets NHP	Mice could be used as a stable and reproducible animal model for the evaluation of vaccines, immune-prophylaxis, and antiviral drugs against SARS-CoV. Golden Syrian and Chinese hamsters have also been evaluated and shown to be excellent models of SARS-CoV infection, owing to their high titer of virus replication in the respiratory tract, associated with diffuse alveolar damage, interstitial pneumonitis, and pulmonary consolidation. Ferrets were found to be susceptible to SARS-CoV infection but could also transmit the virus at low levels by direct contact; need more work. At least six NHP species were tested for SARS; research into the clinical signs of disease in cynomolgus and rhesus macaques gave conflicting results. The first mouse model of MERS infection reported in 2014 involved transducing animals with recombinant adenovirus 5	No info	*Viruses* **2019**, *11*(1), 59; https://doi.org/10.3390/v11010059 *Review* From SARS to MERS, Thrusting Coronaviruses into the Spotlight

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
			encoding human DPP4 (hDPP4) molecules intranasally, and this resulted in replication of MERS-CoV in the lungs. Both hDPP4-KI mouse and the MERS mouse adapted strain provide better tools to explore the pathogenesis of MERS and potential novel treatments. NHPs, such as the rhesus macaques and common marmosets, are useful models for studying the pathogenesis of mild MERS-CoV infection and evaluating novel therapies for humans, although the degree of replication and disease severity vary.		
38	MERS vaccines review (Yong 2019)	NHP (rhesus macaques) Marmosets Camels Mouse	Overall, vaccine candidates against MERS-CoV are mainly based upon the viral spike (S) protein, due to its vital role in the viral infectivity, although several studies focused on other viral proteins such as the nucleocapsid (N) protein, envelope (E) protein, and non-structural protein 16 (NSP16) have also been reported. In general, the potential vaccine candidates can be classified into six types: viral vector-based vaccine, DNA vaccine, subunit vaccine, nanoparticle-based vaccine, inactivated-whole virus vaccine and live-attenuated vaccine, which are discussed in detail. Subunit vaccine is by far the most popular method in the development of MERS vaccine, mostly focusing on the recombinant RBD of the S protein produced in heterologous expression systems. Subunit vaccines, however, are often administered along with adjuvants to boost the immunogenicity. Although the immunogenicity of VLPs-based vaccines could be enhanced by adjuvants, the VLPs themselves can serve as adjuvants which increase the immunogenicity of displayed epitopes, particularly those of smaller ones. Viral vector-based vaccine is one of the most popular approaches in developing MERS vaccines. Two out of the three candidate vaccines which have entered the clinical phase are viral vector vaccines which utilize well-studied virus replication system to	Vaccine candidates against SARS-CoV were initially developed based on the full-length S protein. However, these vaccines were later demonstrated to induce non-neutralizing antibodies which did not prevent MERS-CoV infection, and the immunized animals were not protected from the viral challenge instead they experienced adverse effects like enhanced hepatitis, increased morbidity, and stronger inflammatory responses (Weingartl et al., 2004; Czub et al., 2005). Many potential vaccines against MERS-CoV were also mainly focused on the same full-length S protein, raising a safety concern on the practical	Front Microbiol. 2019 Aug 2;10:1781. doi: 10.3389/fmicb.2019.01781. eCollection 2019. Recent Advances in the Vaccine Development Against Middle East Respiratory Syndrome-Coronavirus

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
			display MERS-CoV antigen, thereby inducing protective immunity against MERS-CoV. DNA vaccine production does not involve virus replication, protein expression and purification, therefore reduce the cost of production. However, administration often requires an external device such as electroporator or gene gun, which eventually increases the cost of immunization. Pathological changes induced in rhesus macaques infected by MERS-CoV were the results of the host inflammatory responses triggered by the virus instead of the direct viral cytolytic activity (Prescott et al., 2018). Common marmoset also demonstrated signs of renal damage as in human cases following MERS-CoV infection, and the viral RNA could be detected in other non-respiratory organs contrary to rhesus macaques (van Doremalen and Munster, 2015; Yeung et al., 2016). Falzarano et al. (2014) also reported that the common marmoset could serve as a partially lethal animal model. MERS-CoV tropism in dromedary camels is limited to the upper respiratory tract, and is less apparent in the lower respiratory tract, contrary to rhesus macaques (Adney et al., 2014). Mice transduced by a viral vector to express human DPP4 (hDPP4) were shown to be susceptible to MERS-CoV infection, manifested by the development of pneumonia and histopathological changes in the lungs. However, viral clearance in these infected mice was observed at day-8 post-infection, failing to recapitulate severe human diseases (Zhao et al., 2014). Later, a more established transgenic mouse model expressing hDPP4 globally was developed, and it was the first lethal animal model available to evaluate MERS-CoV vaccines. Mortality was noted in these mice within days post-infection, and virus dissemination to other organs was observed with exceptionally high titer detected in the lung and brain (Agrawal et al., 2015).	application of these vaccines (Du et al., 2016b). To date, no ADE has been observed in MERS-CoV. Two approaches have been suggested to mitigate the adverse effects of ADE: 1) shielding the non-neutralizing epitopes of the S proteins by glycosylation and 2) immunofocusing that aims to direct the adaptive immune responses to target only the critical neutralizing epitope to elicit a more robust protective immunity (Du et al., 2016a; Okba et al., 2017). Use of IWV as a vaccine in MERS was reported to be associated with hypersensitivity-type lung immunopathologic reaction in the mouse model (Agrawal et al., 2015),	

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			Another transgenic mouse model has been introduced, in which the *hDPP4* gene was inserted into the genome of C57BL/6-mouse at Rosa26 locus using the CRISPR/Cas9 technology. This mouse model, namely R26-hDPP4, when infected by MERS-CoV at low dose, developed severe lung diseases related to acute respiratory symptoms (ARDS) and central nervous system (CNS). In addition, the R26-hDPP4 is also susceptible to infection by a MERS-CoV pseudovirus, serving as an alternative to test MERS-CoV vaccines in the absence of BSL-3 facility (Fan et al., 2018).		
39	Review of MERS MoAbs and vaccines (Xu 2019)	Mouse NHP	Among all the potential targets of MERS-CoV, the spike glycoprotein (S) has been the most well-studied due to its critical role in mediating viral entry and in inducing a protective antibody response in infected individuals. The most notable studies include the recent discoveries of monoclonal antibodies and development of candidate vaccines against the S glycoprotein. Structural characterization of MERS-CoV S protein bound with these monoclonal antibodies has provided insights into the mechanisms of humoral immune responses against MERS-CoV infection.	Hashem and colleagues showed that the adenovirus-based S1 vaccine may pose potential safety concerns because it may induce pulmonary perivascular hemorrhage in a MERS-CoV challenge mouse model, regardless of the its full protection upon lethal viral infection. They also showed that the pulmonary pathology can be mitigated by incorporating CD40L, an immune-modulator therefore potential molecular adjuvant, into the recombinant adenovirus-based vaccine [72].	Emerging Microbes & Infections 2019, VOL. 8 https://doi.org/10.1080/22221751.2019.1624482 Antibodies and vaccines against Middle East respiratory syndrome coronavirus
40	MERS vaccine and treatment review	Mouse NHP	Plasma of convalescent MERS-CoV-infected patients is useful for treatment of MERS-CoV infectionclinically, but it requires a neutralizing antibody titer (e.g., 50% plaque-reduction	Compared with vaccines based on MERS-CoV full-length S protein, which have the	Viruses 2019,11, 60; doi:10.3390/v11010060

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	(Zhou 2019)		neutralization titer:PRNT50)≥1:80 to obtain effective therapeutic results [51–53]. Multiple vaccines described using MERS-CoV spike (S) protein receptor-binding domain (RBD)	potential to attenuate neutralizing activity or enhance immune pathology, vaccines developed from MERS-CoV S-protein RBD are safer, and they do not cause immunological toxicity or eosinophilic immune enhancement [55,99,110,124]. Moreover, RBD-based therapeutic antibodies are generally more potent than non-RBD S1-based or S2-based antibodies [58,104,111]. Hence, RBD-based vaccines and therapeutic antibodies have the potential for further development as effective tools to prevent and treat MERS-CoV infection. Despite their acknowledged advantages, there are some issues associated with RBD-based interventions that need to be addressed. For example, RBD is under a high level of pressure of positive selection, and mutations occur in the RBD-DPP4 binding interface that might reduce the efficacy of	www.mdpi.com/journal/viruses Advances in MERS-CoV Vaccines and Therapeutics Based on the Receptor-Binding Domain

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				these treatments [100,125,126,127]. One possible way to avoid this effect, and to delay the emergence of escape mutants is to combine RBD-targeting therapeutics with those targeting other regions of the S protein, or to combine antibodies recognizing distinct epitopes within the RBD [102,128]. Such combinatorial strategies could also dramatically reduce antibody neutralization doses, providing feasible means to combat the continual threat of MERS-CoV.	
41	Review SARS, MERS (Song 2019)	Mouse NHP	We focus on our current understanding of the epidemiology, pathogenesis, prevention, and treatment of SARS-CoV and MERS-CoV, as well as provides details on the pivotal structure and function of the spike proteins (S proteins) on the surface of each of these viruses. For building up more suitable animal models, we compare the current animal models recapitulating pathogenesis and summarize the potential role of host receptors contributing to diverse host affinity in various species. We outline the research still needed to fully elucidate the pathogenic mechanism of these viruses, to construct reproducible animal models, and ultimately develop countermeasures to	No info	Viruses. 2019 Jan 14;11(1). pii: E59. doi: 10.3390/v11010059. From SARS to MERS, Thrusting Coronaviruses into the Spotlight

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
			conquer not only SARS-CoV and MERS-CoV, but also these emerging coronaviral diseases.		
42	DNA and RNA vaccines discussed, not specific to MERS and SARS (Rauch 2018)		This review discusses viral vector and nucleic acid-based vaccines (DNA and mRNA vaccines) as new approaches that might be able to tackle these challenges to global health.	No info	Front Immunol. 2018 Sep 19;9:1963. doi: 10.3389/fimmu.2018.01963. eCollection 2018. New Vaccine Technologies to Combat Outbreak Situations
43	MERS CoV review (Shokri 2018)		In this review, we have highlighted the major mechanisms of immune evasion strategies of MERS-CoV. We have demonstrated that M, 4a, 4b proteins and Plppro of MERS-CoV inhibit the type I interferon (IFN) and nuclear factor-κB signaling pathways and therefore facilitate innate immune evasion. In addition, nonstructural protein 4a (NSP4a), NSP4b, and NSP15 inhibit double-stranded RNA sensors. Therefore, the mentioned proteins limit early induction of IFN and cause rapid apoptosis of macrophages. MERS-CoV strongly inhibits the activation of T cells with downregulation of antigen presentation. In addition, uncontrolled secretion of interferon ɣ -induced protein 10 and monocyte chemoattractantprotein-1 can suppress proliferation of human myeloid progenitor cells.	No info	J Cell Physiol. 2019 Mar;234(3):2143-2151. doi: 10.1002/jcp.27155. Epub 2018 Aug 26. Modulation of the immune response by Middle East respiratory syndrome coronavirus
44	Mouse models CoV (no vaccines) (Cockrell 2018)	Mouse	In addition to assessing etiologies of known hCoVs, mouse models have clinically predictive value as tools to appraise potential disease phenotypes associated with pre-emergent CoVs. Knowledge of CoV pathogenic potential before it crosses the species barrier into the human population provides a highly	No info	Mammalian Genome (2018) 29:367–383 https://doi.org/10.1007/s00335-018-9760-9

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			desirable preclinical platform for addressing global pathogen preparedness, an overarching directive of the WHO. Although we recognize that results obtained in robust mouse models require evaluation in non-human primates, we focus this review on the current state of hCoV mouse models, their use as tractable complex genetic organisms for untangling complex hCoV–host interactions, and as pathogenesis models for preclinical evaluation of novel therapeutic interventions. Effective mouse models for SARS-CoV and MERS-CoV should minimally be able to recapitulate fatal respiratory disease having pathology similar to that observed in humans. A number of mouse models exhibiting fatal respiratory disease were developed for SARS-CoV and MERS-CoV; however, a single impediment was realized early in model development for MERS-CoV that was not confronted for SARS-CoV. The mouse orthologue of the human receptor for MERS-CoV, dipeptidyl peptidase 4 (DPP4), did not support interaction with the MERS-CoV spike glycoprotein RBD (Cockrell et al. 2014). Therefore, unlike SARS-CoV, commercially available mice were not susceptible to MERS-CoV infection and replication. A recently developed, innovative resource for genetic mapping, called the Collaborative Cross (CC), comprises a panel of recombinant inbred mouse strains containing tractable genetic diversity that approaches the genetic diversity in the human population. Using an octo-parental breeding scheme that includes classical laboratory stains (A/J, C57BL/6J, and 129/SvImJ), mouse models for human diseases (NOD/ShiLtJ for diabetes; NZO/HlLtJ for obesity), and wild-derived mouse strains (CAST/EiJ, PWK/PhJ, and WSB/EiJ), the CC captures 90% of the genetic variation present in the three major mouse subspecies (Mus musculus musculus, Mus musculus domesticus, Mus musculus castaneus) . The CC mouse platform can be used to identify novel mouse models that		Modeling pathogenesis of emergent and pre-emergent human coronaviruses in mice

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			recapitulate human clinical outcomes resulting from pathogenic viruses.		
45	Coronaviruses, no vaccine (Chen 2020		A brief introduction of the general features of coronaviruses and describe various diseases caused by different coronaviruses in humans and animals. This review will help understand the biology and potential risk of coronaviruses that exist in richness in wildlife such as bats. The genome size of CoV (~30kb) is the largest among all RNA viruses, which is almost two times larger than that of the second largest RNA viruses. Based on the phylogenetic tree of CoVs, 2019-nCov is more closely related to bat-SL-CoV ZC45 and bat-SL-CoV ZXC21 and more distantly related to SARS-CoV.		J Med Virol. 2020 Jan 22. doi: 10.1002/jmv.25681. [Epub ahead of print] Emerging coronaviruses: genome structure, replication, and pathogenesis
46	SARS and MERS CoVs pandemic potential (deWit 2016)		This Review highlights the pandemic and epidemic potential of emerging coronaviruses and discusses our current knowledge of the biology of SARS-CoV and MERS-CoV, including their transmission, their pathogenesis and the development of medical countermeasures. Key features of these viruses are the dominance of nosocomial transmission, and pathogenesis that is driven by a combination of viral replication in the lower respiratory tract and an aberrant host immune response. Similarly to all viruses in the order *Nidovirales*, SARS-CoV and MERS-CoV have a unique coding strategy: two-thirds of the viral RNA is translated into two large polyproteins, and the remainder of the viral genome is transcribed into a nested set of subgenomic mRNAs. Human-to-human transmission of SARS-CoV and MERS-CoV occurs mainly through nosocomial transmission; 43.5–100% of MERS cases in individual outbreaks were linked to hospitals, and very similar observations were made for some of the SARS clus-ters35,36.	One concern of vaccination in humans is vaccine-mediated enhancement of disease, a process in which the disease following infection is more severe in vaccinated individuals than in unvaccinated individuals. Although this was observed in only a small subset of vaccine studies that were carried out for SARS-CoV136 and has not yet been observed in any of the published MERS-CoV vaccine studies, it is an important concern. Moreover, it is unclear who to vaccinate against MERS-CoV, as healthy	Nat Rev Microbiol. 2016 Aug;14(8):523-34. doi: 10.1038/nrmicro.2016.81. Epub 2016 Jun 27. Review. PMID: 27344959 SARS and MERS: recent insights into emerging coronaviruses

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
			Transmission between family members occurred in only 13–21% of MERS cases and 22–39% of SARS cases. Transmission of MERS-CoV between patients was the most common route of infection (62–79% of cases), whereas for SARS-CoV, infection of health care workers by infected patients was very frequent (33–42%)35. The predominance of nosocomial transmission is probably due to the fact that substantial virus shedding occurs only after the onset of symptoms37,38, when most patients are already seeking medical care39. An analysis of hospital surfaces after the treatment of patients with MERS showed the ubiquitous presence of viral RNA in the environment for several days after patients no longer tested positive40. Moreover, many patients with SARS or MERS were infected through super spreaders14,35,37,41–43. The immune response is essential for the resolution of an infection, but it can also result in immunopathogenesis. One indication that immunopathogenesis may contribute to SARS was the observation that viral loads were found to be decreasing while disease severity increased39,47. It is unclear whether a similar trend applies to MERS48,49. Moreover, progression to acute respiratory distress syndrome (ARDS) is associated with the upregulation of pro-inflammatory cytokines and chemokines, particularly interleukin-1β (IL-1β), IL-8, IL-6, CXC-chemokine ligand 10 (CXCL10) and CC-chemokine ligand 2 (CCL2)50,51; increased plasma levels of these molecules have been detected in patients with SARS52–55. Retrospective longitudinal studies in patients who recovered from SARS versus those who succumbed to the disease have shown an early expression of interferon-α (IFNα), IFNγ, CXCL10, CCL2 and proteins that are encoded by IFN-stimulated genes (ISGs) in all	individuals seem to be at little risk of severe disease. Older patients or patients with underlying disease, who have the highest risk of severe MERS, would be important target populations. However, vaccination in such patients can be problematic owing to their poor immune responses, as has been established for influenza virus141. In addition, vaccination of people with a high risk of exposure to MERS-CoV, such as health care workers, slaughterhouse workers and camel herders, is advisable142.	

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			patients, but only patients who survived then had gene expression profiles that are indicative of the development of an adaptive immune response. By contrast, patients who succumbed maintained high levels of CXCL10, CCL2 and ISG-encoded proteins, whereas spike-specific antibodies were present at low levels or were absent56, which suggests that severe disease is related to the lack of a switch from an innate immune response to an adaptive immune response. The involvement of the host immune response in the pathogenesis of SARS, and most likely also that of MERS, suggests that drugs which inhibit viral replication will need to be combined with treatments that control detrimental immune responses. SARS-CoV and MERS-CoV use several strategies to avoid the innate immune response.		
47	Review of coronaviruses No vaccine (Fehr and Perlman 2015)		Vaccine development for coronaviruses faces many challenges [107]. First, for mucosal infections, natural infection does not prevent subsequent infection, and so vaccines must either induce better immunity than the original virus or must at least lessen the disease incurred during a secondary infection. Second, the propensity of the viruses to recombine may pose a problem by rendering the vaccine useless and potentially increasing the evolution and diversity of the virus in the wild [108]. Finally, it has been shown in FIPV that vaccination with S protein leads to enhanced disease [109]. Despite this, several strategies are being developed for vaccine development to reduce the likelihood of recombination, for instance by making large deletions in the nsp1 [110] or E proteins [111], rearranging the 3' end of the genome [112], modifying the TRS sequences [113], or using mutant viruses with abnormally high mutation rates that	No further info	Methods Mol Biol. 2015;1282:1-23. doi: 10.1007/978-1-4939-2438-7_1. Coronaviruses: an overview of their replication and pathogenesis

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
			significantly attenuate the virus [114].		
48	Human MERS disease No vaccine (Drosten 2014)		We studied 26 index patients with MERS-CoV infection and their 280 household contacts. The median time from the onset of symptoms in index patients to the latest blood sampling in contact patients was 17.5 days (range, 5 to 216; mean, 34.4). Probable cases of secondary transmission were identified on the basis of reactivity in two reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays. Among the 280 household contacts of the 26 index patients, there were 12 probable cases of secondary transmission (4%; 95% confidence interval, 2 to 7). Of these cases, 7 were identified by means of RT-PCR, all in samples obtained within 14 days after the onset of symptoms in index patients, and 5 were identified by means of serologic analysis, all in samples obtained 13 days or more after symptom onset in index patients. Probable cases of secondary transmission occurred in 6 of 26 clusters (23%). Serologic results in contacts who were sampled 13 days or more after exposure were similar to overall study results for combined RT-PCR and serologic testing. The rate of secondary transmission among household contacts of patients with MERS-CoV infection has been approximately 5%. Our findings suggest that persons in the first few decades of life without coexisting illnesses may be able to carry low levels of MERS-CoV RNA without obvious symptoms. Asymptomatic, RT-PCR–positive health care workers were identified in a recent outbreak of MERS in Jeddah.	No info	N Engl J Med 2014;371:828-35. DOI: 10.1056/NEJMoa1405858 Transmission of MERS-Coronavirus in Household Contacts
49	Epi SARS, MERS , flu on surfaces No vaccine		SARS-CoV, MERS-CoV, and influenza virus can survive on surfaces for extended periods, sometimes up to months.	No info	J Hosp Infect. 2016 Mar;92(3):235-50. doi:

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
	(Otter 2016)		The importance of indirect contact transmission (involving contamination of inanimate surfaces) is uncertain compared with other transmission routes, principally direct contact transmission (independent of surface contamination), droplet, and airborne routes. However, influenza virus and SARS-CoV may be shed into the environment and be transferred from environmental surfaces to hands of patients and healthcare providers. Emerging data suggest that MERS-CoV also shares these properties.		10.1016/j.jhin.2015.08.027. Epub 2015 Oct 3. Transmission of SARS and MERS coronaviruses and influenza virus in healthcare settings: the possible role of dry surface contamination
50	MERS CoV No vaccine (Mackay 2015)		In humans, MERS is mostly known as a lower respiratory tract (LRT) disease involving fever, cough, breathing difficulties and pneumonia that may progress to acute respiratory distress syndrome, multiorgan failure and death in 20 % to 40 % of those infected. However, MERS-CoV has also been detected in mild and influenza-like illnesses and in those with no signs or symptoms. Older males most obviously suffer severe disease and MERS patients often have comorbidities. Compared to severe acute respiratory syndrome (SARS), another sometimes- fatal zoonotic coronavirus disease that has since disappeared, MERS progresses more rapidly to respiratory failure and acute kidney injury (it also has an affinity for growth in kidney cells under laboratory conditions), is more frequently reported in patients with underlying disease and is more often fatal. Most human cases of MERS have been linked to lapses in infection prevention and control (IPC) in healthcare settings, with approximately 20 % of all virus detections reported among healthcare workers (HCWs) and higher exposures in those with occupations that bring them into close contact	No info	Virol J. 2015 Dec 22;12:222. doi: 10.1186/s12985-015-0439-5. MERS coronavirus: diagnostics, epidemiology and transmission

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
			with camels. Sero-surveys have found widespread evidence of past infection in adult camels and limited past exposure among humans.		
51	CoV pathogenesis (Menachery 2017)		In this review, we explore the host and viral dynamics that shape these CoV populations for survival, amplification, and possible emergence in novel hosts.	No info	Curr Opin Virol. 2017 Apr;23:1-7. doi: 10.1016/j.coviro.2017.01.002. Epub 2017 Mar 31. Jumping species a mechanism for coronavirus persistence and survival.
52	Adenovirus-based vaccine expressing MERS-CoV S1-CD40L fusion protein (Hashem 2019)	Mouse (hDPP4 Tg^+)	Immunization of hDPP4 Tg^+ mice with a single dose of rAd5-S1/F/CD40L elicited as robust and significant specific immunoglobulin G and neutralizing antibodies as those induced with 2 doses of rAd5-S1. After MERS-CoV challenge, both vaccines conferred complete protection against morbidity and mortality, as evidenced by significantly undetectable/reduced pulmonary viral loads compared to the control group.	However, rAd5-S1– but not rAd5-S1/F/CD40L–immunized mice exhibited marked pulmonary perivascular hemorrhage post–MERS-CoV challenge despite the observed protection. Incorporation of CD40L into rAd5-based MERS-CoV S1 vaccine targeting molecule and molecular adjuvants not only enhances immunogenicity and efficacy but also prevents inadvertent pulmonary pathology after viral challenge, thereby offering a promising strategy to enhance safety and potency of vaccines.	J Infect Dis. 2019 Mar 26. doi:10.1093/infdis/jiz137. PubMed PMID: 30911758 A highly immunogenic, protective and safe adenovirus-based vaccine expressing MERS-CoV S1-CD40L fusion protein in transgenic human DPP4 mouse model.

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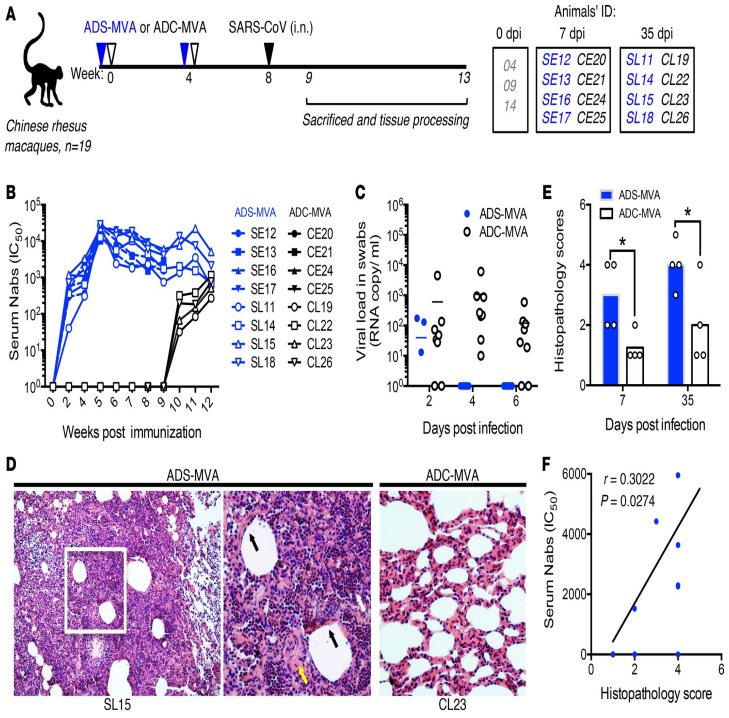
53	MVA-SARS -CoV glycoprotein S (Liu 2019)	NHP (Chinese rhesus macaques)	An extensive set of experiments are described to elucidate mechanisms for enhanced lung pathology following administration of an MVA vaccine with SARS glucoprotein S and what happens when immune sera from immunized macaques are administered prior to live virus challenge. 	In SARS-CoV/macaque models, we determined that anti–spike IgG (S-IgG), in productively infected lungs, causes severe ALI by skewing inflammation-resolving response. Alveolar macrophages underwent functional polarization in acutely infected macaques, demonstrating simultaneously both proinflammatory and wound-healing characteristics. The presence of S-IgG prior to viral clearance, however, abrogated wound-healing responses and promoted MCP1 and IL-8 production and proinflammatory monocyte/macrophage recruitment and accumulation. Patients who eventually died of SARS displayed similarly accumulated pulmonary proinflammatory, absence of wound-healing macrophages, and faster neutralizing antibody responses. Their sera enhanced SARS-CoV–induced MCP1 and IL-8	JCI Insight. 2019; 4(4):e123158. https://doi.org/10.1172/jci.insight.123158 Anti–spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
				production by human monocyte–derived wound-healing macrophages, whereas blockade of FcγR reduced such effects. Our findings reveal a mechanism responsible for virus-mediated ALI, define a pathological consequence of viral specific antibody response, and provide a potential target for treatment of SARS-CoV or other virus-mediated lung injury.	
54	SARS-CoV and SARS-CoV-2 in vitro, no vaccine (Tian 2020)	None	Here, we report for the first time that a SARS-CoV-specific human monoclonal antibody, CR3022, could bind potently with 2019-nCoV RBD (KD of 6.3 nM). The epitope of CR3022 does not overlap with the ACE2 binding site within 2019-nCoV RBD. These results suggest that CR3022 may have the potential to be developed as candidate therapeutics, alone or in combination with other neutralizing antibodies, for the prevention and treatment of 2019-nCoV infections. Interestingly, some of the most potent SARS-CoV-specific neutralizing antibodies (e.g. m396, CR3014) that target the ACE2 binding site of SARS-CoV failed to bind 2019-nCoV spike protein, implying that the difference in the RBD of SARS-CoV and 2019-nCoV has a critical impact for the cross-reactivity of neutralizing antibodies, and that it is still necessary to develop novel monoclonal antibodies that could bind specifically to 2019-nCoV RBD.	No info	Emerg Microbes Infect. 2020 Dec;9(1):382-385. doi: 10.1080/22221751.2020.1729069. Tian X, Li C, Huang A, Xia S, Lu S, Shi Z, Lu L, Jiang S, Yang Z[3] Wu Y, Ying T Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-

#	Vaccine(s) (1st Author Yr Published)	Animal Model	Findings	Enhanced Disease on Challenge Post-vaccination?	Reference
					specific human monoclonal antibody.
55	MERS, SARS and SARS-CoV-2 pathogenesis review, no vaccine (Liu 2020)	None	Description of MErS and SARS features then the following re: SARS-CoV-2: The genetic sequence analysis revealed that the 2019-nCoV belongs to theβ-coronavirus genus, with a 79.0% nucleotide identity to SARS-CoV and 51.8% identity to MERS-CoV 34. Furthermore, it has been reported that nCoV-2019 is 96% identical across the entire genome to a bat coronavirus 35. Inoculation of the 2019-nCoV onto surface layers of human airway epithelial cells in vitro causes cytopathic effects and cessation of cilium beating of the cells 5. The 2019-nCoV infection was of clustering onset, is more likely to affect older males with comorbidities, and can result in severe and even fatal respiratory diseases 36,37. The major clinical symptoms resulting from 2019-nCoV infection at the prodromal phase include fever, dry cough, myalgia, fatigue, and diarrhea38. Many patients also developed dyspnea and lymphopenia. Complications of 2019-nCoV infections included acute respiratory distress syndrome, RNAaemia, acute cardiac injury, and secondary (super-)infections 38. All reported cases, including asymptomatic patients, had abnormal findings concerning the chest CT as indicated by bilateral ground glass opacity 6,38. The prototypical findings of chest CT images of seriously ill patients requiring ICU admission were bilateral multiple lobular and subsegmental areas of consolidation38. Initial plasma IL-1β, IL-1Rα, IL-7, IL-8, IL-9, IL-10, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNF-α, and VEGF	No info	J Med Virol. 2020 Feb 13. doi: 10.1002/jmv.25709. [Epub ahead of print] Liu J, Zheng X, Tong Q, Li W, Wang B, Sutter K, Trilling M, Lu M, Dittmer U, Yang D Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV.

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			concentrations were higher in 2019-nCoV-infected patients as compared to healthy controls. Moreover, ICU patients showed higher plasma levels of IL-2, IL-7, IL-10, GSCF, IP10, MCP1, MIP1A, and TNF-α than non-ICU patients 38. These results suggest that immunopathology may also play a relevant role in the development of disease severity.		
56	SARS and MERS CoV review of immune response to infection, no vaccine (Li 2020)	None	In this review, we provide an update on CoV infections and relevant diseases, particularly the host defense against CoV-induced inflammation of lung tissue, as well as the role of the innate immune system in the pathogenesis and clinical treatment. By comparing T-cell-deficient BALB/c mice (transduced by ad5-hdp4) with controls and B-cell-deficient mice, some researchers determined that T cells could survive in the infected lungs and destroy the infected cells.75 The depletion of CD8+ T cells does not affect and delay viral replication at the time of infection with SARS-CoV.77,78 Depletion of CD4+ T cells is associated with reduced pulmonary recruitment of lymphocytes and neutralizing antibody and cytokine production, resulting in a strong immune-mediated interstitial pneumonitis and delayed clearance of SARS-CoV from lungs.79 MERS-CoV induces T cell apoptosis by activating the intrinsic and extrinsic apoptosis pathways. A novel BH3-like region located in the C-terminal cytosolic domain of SARS-CoV protein mediates its binding to Bcl-xL and induced T-cell apoptosis.83 During the later stage of infection, depletion of T cells having antiviral effects may prolong the infection and promote viral survival.84 SARS-CoV-specific T cells have been screened in SARS convalescent patients.	No info	J Med Virol. 2020 Jan 25. doi: 10.1002/jmv.25685. [Epub ahead of print] Li G, Fan Y Lai Y Han T, Li Z, Zhou P, Pan P, Wang W, Hu D, Liu X, Zhang Q, Wu J. Coronavirus infections and immune responses.

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			All the detected memory T cell responses are directed at SARS-CoV structural proteins. Two CD8+T cell responses to SARS-CoV membrane (M) and Nucleocapsid (N) protein are characterized by measuring their HLA restriction and minimal T cell epitope regions. Further, these reactions are found to last up to 11 years after infection. Absence of cross-reactivity of these CD8+T cell responses against the MERS-CoV is also demonstrated.78 Reports show that humoral immunity is essential to control the persistent phase of CoV infection. SARS-CoV infection activates the complement pathway and complement signaling contributes to disease.92		
57	No vaccine, EM study SARS-CoV spike (Gui, 2017)	In vitro	We report here the cryo-EM structure determination of the SARS-CoV S glycoprotein trimer in four different conformations. Structural analyses revealed that these conformations are different in the position of one C-terminal domain 1 (CTD1), which functions as the RBD of the S glycoprotein trimer. Structural comparisons further indicated that a “down” to “up” positional change of the CTD1 switches the S glycoprotein trimer from receptor-binding inactive to active state, which is a prerequisite for the binding of SARS-CoV receptor ACE2 and for the neutralization by monoclonal antibodies.	No info	Cell Res. 2017 Jan;27(1):119-129. doi: 10.1038/cr.2016.152. Epub 2016 Dec 23. Gui M, Song W, Zhou H, Xu J, Chen S, Xiang Y, Wang X. Cryo-electron microscopy structures of the SARS-CoV spike glycoprotein reveal a prerequisite conformational state for receptor binding.

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58	No vaccine, in vitro studies using survivor SARS and MERS patient antibodies (Walls, 2019)		The trimeric spike transmembrane glycoprotein S mediates entry into host cells and is the major target of neutralizing antibodies. To understand the humoral immune response elicited upon natural infections with coronaviruses, we structurally characterized the SARSCoV and MERS-CoV S glycoproteins in complex with neutralizing antibodies isolated from human survivors. Although the two antibodies studied blocked attachment to the host cell receptor, only the anti-SARS-CoV S antibody triggered fusogenic conformational changes via receptor functional mimicry. These results provide a structural framework for understanding coronavirus neutralization by human antibodies and shed light on activation of coronavirus membrane fusion, which takes place through a receptor-driven ratcheting mechanism. In summary, coronaviruses appear to have evolved a fine-tuned balance between masking of the RBM, to limit neutralization by the humoral host immune response, and their necessary exposure, to enable receptor recognition and infection of host cells.	No info	Cell. 2019 Feb 21;176(5):1026-1039.e15. doi: 10.1016/j.cell.2018.12.028. Epub 2019 Jan 31. Walls AC, Xiong X, Park YJ, Tortorici MA, Snijder J, Quispe J, Cameroni E, Gopal R, Dai M, Lanzavecchia A, Zambon M, Rey FA, Corti D, Veesler D. Unexpected Receptor Functional Mimicry Elucidates Activation of Coronavirus Fusion.

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59	No vaccines, animal model SARS-CoV-2 (Bao, 2020)	Mice, hACE2 transgenic. 6-11-month male and female WT mice (WT-HB-01) and hACE2 mice (ACE2-HB-01)	Based on angiotensin converting enzyme 2 (ACE2) as the cell entry receptor of SARS-CoV, we used the hACE2 transgenic mice infected with SARS-CoV-2 to study the pathogenicity of the virus. Weight loss and virus replication in lung were observed in hACE2 mice infected with SARS-CoV-2. The typical histopathology was interstitial pneumonia with infiltration of significant lymphocytes and monocytes in alveolar interstitium, and accumulation of macrophages in alveolar cavities. Viral antigens were observed in the bronchial epithelial cells, alveolar macrophages and alveolar epithelia. The phenomenon was not found in wild type mice with SARS-CoV-2 infection. The pathogenicity of SARS-CoV-2 in hACE2 mice was clarified and the Koch's postulates were fulfilled as well, and the mouse model may facilitate the development of therapeutics and vaccines against SARS-CoV-2. **The pathogenicity of SARS-CoV-2 seems mild compared to SARS-CoV in mice, the latter caused extrapulmonary organ damage, includes brain, kidney, intestine, heart and liver, furthermore, the neurons are susceptible for SARS-CoV infection, and cerebral vasculitis and hemorrhage were observed in hACE2 transgenic mice10,11.** **However, only interstitial pneumonia was observed in SARS-CoV-2-infected hACE2 mice, implying the disparity in pathogenicity of the coronavirus.**	No info	bioRxiv preprint doi: https://doi.org/10.1101/2020.02.07.939389. Linlin Bao, Wei Deng, Baoying Huang, et al The Pathogenicity of SARS-CoV-2 in hACE2 Transgenic Mice

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60	No vaccine, comparison sequence data (Ahmed, 2020)		By screening the experimentally determined SARS-CoV-derived B cell and T cell epitopes in the immunogenic structural proteins of SARS-CoV, we identified a set of B cell and T cell epitopes derived from the spike (S) and nucleocapsid (N) proteins that map identically to SARS-CoV-2 proteins. As no mutation has been observed in these identified epitopes among the 120 available SARS-CoV-2 sequences (as of 21 February 2020), immune targeting of these epitopes may potentially offer protection against this novel virus. For the T cell epitopes, we performed a population coverage analysis of the associated MHC alleles and proposed a set of epitopes that is estimated to provide broad coverage globally, as well as in China. Our findings provide a screened set of epitopes that can help guide experimental efforts towards the development of vaccines against SARS-CoV-2. We found that only 23% and 16% of known SARS-CoV T cell and B cell epitopes map identically to SARS-CoV-2, respectively, and with no mutation having been observed in these epitopes among the available SARS-CoV-2 sequences (as of 21 February 2020). This provides a strong indication of their potential for eliciting a robust T cell or antibody response in SARS-CoV-2.	No info	Viruses. 2020 Feb 25;12(3). pii: E254. doi: 10.3390/v12030254. Ahmed SF, Quadeer AA, McKay MR. Preliminary Identification of Potential Vaccine Targets for the COVID-19 Coronavirus (SARS-CoV-2) Based on SARS-CoV Immunological Studies.

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61	No vaccine, case report COVID-19 (Lan 2020)		Four patients (HCWs) with COVID-19 who met criteria for hospital discharge or discontinuation of quarantine in China (absence of clinical symptoms and radiological abnormalities and 2 negative RT-PCR test results) had positive RT-PCR test results 5 to 13 days later. These findings suggest that at least a proportion of recovered patients still may be virus carriers. Although no family members were infected, all reported patients were medical professionals and took special care during home quarantine.	asymptomatic infection post-quarantine	JAMA. 2020 Feb 27. doi: 10.1001/jama.2020.2783. [Epub ahead of print] Lan L, Xu D, Ye G, Xia C, Wang S, Li Y, Xu H Positive RT-PCR Test Results in Patients Recovered From COVID-19.
62	No vaccine, review SARS, MERS, COVID-19 (Li, 2020)	Mice, transgenic	SARS-CoV-2 shares highly homological sequence with SARS-CoV, and causes acute, highly lethal pneumonia (COVID-19) with clinical symptoms similar to those reported for SARS-CoV and MERS-CoV. The most characteristic symptom of COVID-19 patients is respiratory distress, and most of the patients admitted to the intensive care could not breathe spontaneously. Additionally, some COVID-19 patients also showed neurologic signs such as headache, nausea and vomiting. Increasing evidence shows that coronaviruses are not always confined to the respiratory tract and that they may also invade the central nervous system inducing neurological diseases. The infection of SARS-CoV has been reported in the brains from both patients and experimental animals, where the brainstem was heavily infected. Furthermore, some coronaviruses have been demonstrated able to spread via a synapse-connected route to the medullary cardiorespiratory center from the mechano- and chemoreceptors in the lung and lower respiratory airways.		J Med Virol. 2020 Feb 27. doi: 10.1002/jmv.25728. [Epub ahead of print] Li YC[1], Bai WZ[2], Hashikawa T[3]. The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients.

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			In light of the high similarity between SARS-CoV and SARS-CoV2, it is quite likely that the potential invasion of SARS-CoV2 is partially responsible for the acute respiratory failure of COVID-19 patients. Awareness of this will have important guiding significance for the prevention and treatment of the SARS-CoV-2-induced respiratory failure. Experimental studies using transgenic mice further revealed that either SARS-CoV 30 or MERS-COV 11, when given intranasally, could enter the brain, possibly via the olfactory nerves, and thereafter rapidly spread to some specific brain areas including thalamus and brainstem. It is noteworthy that in the mice infected with low inoculum doses of MERS-CoV virus particles were detected only in the brain, but not in the lung, which indicates that the infection in the CNS was more important for the high mortality observed in the infected mice 11. Among the involved brain areas, the brainstem has been demonstrated to be heavily infected by SARS-CoV 30, 35 or MERS-CoV 11. The exact route by which SARS-CoV or MERS-COV enters the CNS is still not reported. However, hematogenous or lymphatic route seems impossible, especially in the early stage of infection, since almost no virus particle was detected in the non-neuronal cells in the infected brain areas 32-34. On the other hand, increasing evidence shows that CoVs may first invade peripheral nerve terminals, and then gain access to the CNS via a synapse-connected route 9-10, 19, 36 . The trans-synaptic transfer has been well documented for other coronaviruses, such as HEV67 9-10, 18-19 and avian bronchitis virus 36-37.		

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63	No vaccine, brief review supporting use of convalescent plasma COVID-19 (Chen, 2020)		Convalescent plasma or immunoglobulins have been used as a last resort to improve the survival rate of patients with SARS whose condition continued to deteriorate despite treatment with pulsed methylprednisolone. Moreover, several studies showed a shorter hospital stay and lower mortality in patients treated with convalescent plasma than those who were not treated with convalescent plasma.2–4 In 2014, the use of convalescent plasma collected from patients who had recovered from Ebola virus disease was recommended by WHO as an empirical treatment during outbreaks.5 A protocol for the use of convalescent plasma in the treatment of Middle East respiratory syndrome coronavirus was established in 2015.6 In terms of patients with pandemic 2009 influenza A H1N1 (H1N1pdm09) virus infection, a prospective cohort study by Hung and colleagues showed a significant reduction in the relative risk of mortality (odds ratio 0·20 [95% CI 0·06–0·69], p=0·01) for patients treated with convalescent plasma.7 Additionally, in a subgroup analysis, viral load after convalescent plasma treatment was significantly lower on days 3, 5, and 7 after intensive care unit admission. No adverse events were observed. A multicentre, prospective, double-blind, randomised controlled trial by Hung and colleagues showed that using convalescent plasma from patients who recovered from the influenza A H1N1pdm09 virus infection to treat patients with severe influenza A H1N1 infection was associated with a lower viral load and reduced mortality within 5 days of symptom onset.8 A meta-analysis by Mair-Jenkins and colleagues showed that the mortality was reduced after receiving various doses of convalescent plasma in patients with severe acute respiratory infections, with no adverse events or complications after treatment.9	No info	Lancet Infect Dis. 2020 Feb 27. pii: S1473-3099(20)30141-9. doi: 10.1016/S1473-3099(20)30141-9. [Epub ahead of print] Chen L, Xiong J, Bao L, Shi Y Convalescent plasma as a potential therapy for COVID-19.

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			Another meta-analysis by Luke and colleagues identified eight studies involving 1703 patients with 1918 influenza pneumonia from 1918 to 1925 who received an infusion of influenza-convalescent human blood products, which showed a pooled absolute reduction of 21% (95% CI 15–27; p<0.001) in the overall case fatality rate at low risk of bias.		
64	Avian infectious bronchitis virus (IBV) QX genotype (GI-19 lineage) S1 subunit replacing a Mass + 793B based vaccination (Franzo, 2019)	Chickens (broiler in Italy)	Infectious bronchitis virus (IBV) is a widespread avian coronavirus, whose control relies mainly on extensive vaccine administration. Unfortunately, the continuous emergence of new vaccine-immunity escaping variants prompts the development of new vaccines. In the present work, a molecular epidemiology study was performed to evaluate the potential role of homologous vaccination in driving IBV evolution. This was undertaken by assessing IBV viral RNA sequences from the ORF encoding the S1 portion of viral surface glycoprotein (S) before and after the introduction of a new live vaccine on broiler farms in northern-Italy. The results of several biostatistics analyses consistently demonstrate the presence of a higher pressure in the post-vaccination period. Natural selection was detected essentially on sites located on the protein surface, within or nearby domains involved in viral attachment or related functions. This evidence strongly supports the action of vaccine-induced immunity in conditioning viral evolution, potentially leading to the emergence of new vaccine-escape variants. The great plasticity of rapidly-evolving RNA-viruses in response to human intervention, which extends beyond the poultry industry, is demonstrated, claiming further attention due to their relevance for animal and especially human health.	No info	Vet Res. 2019 Nov 9;50(1):92. doi: 10.1186/s13567-019-0713-4. Franzo G, Legnardi M, Tucciarone CM, Drigo M, Martini M, Cecchinato M. Evolution of infectious bronchitis virus in the field after homologous vaccination introduction.

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			IBV vaccine immunity is not sterilizing and a certain viral persistence in vaccinated animals is possible [42]. The scenario is further worsened by the typically partial coverage achieved by routine vaccination protocols in field conditions that, although usually effective in preventing clinical outbreaks and reducing the infectious pressure, facilitates the circulation of field viruses in a partially immunized population [21, 43]. A previous study based on a phylodynamic approach, performed in the same geographic area and timeframe, demonstrated the benefits of the homologous vaccination introduction in reducing viral population size and outbreak frequency [21]. Nevertheless, the IBV QX genotype has continued to circulate in Italy.		
65	SARS-CoV-2 patient samples, sequencing (Shen, 2020)		We have conducted metatranscriptome sequencing for the bronchoalveolar lavage fluid of eight SARS-CoV-2 patients, 25 community-acquired pneumonia (CAP) patients, and 20 healthy controls. The median number of intra-host variants was 1-4 in SARS-CoV-2 infected patients, which ranged between 0 and 51 in different samples. T he distribution of variants on genes was similar to those observed in the population data (110 sequences). However, very few intra-host variants were observed in the population as polymorphism, implying either a bottleneck or purifying selection involved in the transmission of the virus, or a consequence of the limited diversity represented in the current polymorphism data. Although current evidence did not support the transmission of intra-host variants in a person-to-person spread, the risk should not be overlooked.	No info	Clin Infect Dis. 2020 Mar 4. pii: ciaa203. doi: 10.1093/cid/ciaa203. [Epub ahead of print] Shen Z, Xiao Y, Kang L, Ma W, Shi L, Zhang L, Zhou Z, Yang J, Zhong J, Yang D, Guo L, Zhang G, Li H, Xu Y, Chen M, Gao Z, Wang J, Ren L, Li M. Genomic diversity of SARS-CoV-2 in Coronavirus Disease 2019 patients

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			The microbiota in SARS-CoV-2 infected patients was similar to those in CAP, either dominated by the pathogens or with elevated levels of oral and upper respiratory commensal bacteria. SARS-CoV-2 evolves in vivo after infection, which may affect its virulence, infectivity, and transmissibility. Although how the intra-host variant spreads in the population is still elusive, it is necessary to strengthen the surveillance of the viral evolution in the population and associated clinical changes.		