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Research paper

Animal experiments show impact of vaccination on reduction of SARS-CoV-2 virus circulation: A model for vaccine development?

J. Vandeputte [a,b,*], P. Van Damme [c], J. Neyts [d], J.C. Audonnet [e], M. Baay [f], P. Neels [a,b]

[a] International Alliance for Biological Standardization, Geneve, Switzerland
[b] International Alliance for Biological Standardization Europe, Lyon, France
[c] Centre for the Evaluation of Vaccination and Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp, Belgium
[d] Rega Institute for Medical Research, University of Leuven, Leuven, Belgium
[e] Boehringer Ingelheim Animal Health, Saint Priest, France
[f] P95 Epidemiology & Pharmacovigilance, Leuven, Belgium

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ABSTRACT

Background: In the pre-clinical phase, SARS-CoV-2 vaccines were tested in animal models, including exposure trials, to investigate protection against SARS-CoV-2. These studies paved the way for clinical development. The objective of our review was to provide an overview of published animal exposure results, focussing on the capacity of vaccines to reduce/prevent viral shedding.
Method: Using Medline, we retrieved eighteen papers on eight different vaccine platforms in four animal models. Data were extracted on presence/absence of viral RNA in nose, throat, or lungs, and neutralizing antibody levels in the blood.
Results: All vaccines showed a tendency of reduced viral load after exposure. Particularly nasal swab results are likely to give an indication about the impact on virus excretion in the environment. Similarly, the reduction or prevention of viral replication in the bronchoalveolar environment might be related with disease prevention, explaining the high efficacy in clinical trials.
Discussion: Although it remains difficult to compare the results directly, the potential for a strong reduction of transmission was shown, indicating that the animal models predicted what is observed in the field after large scale human vaccination. This merits further attention for standardization of exposure experiments, with the intention to speed up future vaccine development.

1. Introduction

SARS-CoV-2 has overwhelmed the globe in less than one year with more than 150 million known infections globally and a death toll due to COVID-19 exceeding 3.2 million deaths.[1] The SARS-CoV-2 viral genome was published on January 11, 2020 (GenBank accession number MN908947) [1]. The use of new platform technologies, particularly mRNA and recombinant vector technology [2], the result of decades of fundamental research and development investments, greatly facilitated rapid vaccine development. To assure complete coverage of the almost 8 billion people of this planet, many vaccines and vaccine production sites will be needed. The standardization effort developed by WHO, CEPI and GAVI, the Vaccine Alliance, merits strong support [3].

A number of vaccines has reached conditional market authorization [4] or emergency use authorization [5], while many others are in pre-clinical or in clinical development phase. Phase III studies revealed high efficacy against disease and hospitalization and good safety profiles. Real-world data with authorized vaccines [6,7] revealed that vaccination markedly reduced viral load in vaccinated individuals which may thus likely impact transmission. This was further substantiated in recent studies looking at transmissibility from vaccinated healthcare workers to their family members in Scotland (14 days after dose 1, 30% reduction) [8] and in England (14–21 days after dose 1, 38–49% reduction) [9].

A non-human primate model based on rhesus macaques [10,11] and cynomolgus macaques [11,12], and a small animal model using ferrets [13] or Syrian golden hamsters [14] were developed by many groups for SARS-CoV-2 infection and countermeasure development. A number of

* Corresponding author. International Alliance for Biological Standardization – IABS, Switzerland.
E-mail address: joris.vandeputte@iabs.org (J. Vandeputte).

[1] Johns Hopkins; https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6.

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vaccines, including mRNA vaccines (Pfizer BioNTech, Moderna and Curevac), Adeno vector recombinant vaccines (AstraZeneca and J&J), Yellow fever vector recombinant vaccines (University of Leuven, Belgium, Regavax), Measles recombinant vaccines, nanoparticle vaccines, subunit vaccines, and purified inactivated vaccines were used in these animal models. Here we provide a concise overview of published results, in which we focus particularly on the capacity of the vaccines to reduce or prevent viral shedding following exposure.

2. Methods

A review was performed for SARS-CoV-2 exposure studies in animal models, after vaccination with COVID-19 vaccine candidates. We searched MEDLINE (PubMed, which includes bioRxiv) for relevant articles. Mammal models were included, based on susceptibility to SARS-CoV-2 infection [15–19]. Search terms used were: (cat OR dog OR ferret OR cynomolgus macaque OR rhesus macaque OR African green monkey OR Syrian hamster) AND SARS-CoV-2 AND infection AND vaccine. Citations from eligible articles were also searched to identify other relevant studies.

The following data were extracted from eligible studies: first author, journal name, publication year, animal model, vaccine platform, vaccine name, vaccine route of administration, vaccine dose, vaccine schedule, exposure strain, exposure dose, exposure route of administration, exposure schedule, method to detect neutralizing antibodies, geometric mean titer in control animals, geometric mean titer in vaccinated animals, geometric mean titer in human convalescent sera, neutralizing antibodies ratio vaccinated vs control, neutralizing antibodies ratio vaccinated vs human convalescent serum, method to detect (subgenomic) RNA, viral load in control animals, number of controls animals positive, viral load in vaccinated animals, number of vaccinated animals positive.

To meet the objectives of the study the focus was on presence or absence of viral RNA in affected organs (nose, throat, lungs) and neutralizing antibody levels in the blood.

3. Results

Our search retrieved 123 studies, of which 18 were eligible for extraction. Distribution by animal model and vaccine type is shown in Table 1. An overview of all data extracted is provided in Supplementary Table S1.

Table 1
Distribution of studies by animal model and vaccine type.

Vaccine \ Model	Syrian hamster	Ferret	Rhesus macaque	Cynomolgus macaque
mRNA	Rauch 2021		Vogel 2020, Corbett 2020, Rauch 2020	
Adenovirus	Tostanoski 2020		Van Doremalen 2020, Van Doremalen 2021, Mercado 2020, Feng 2020	
Yellow fever	Sanchez-Felipe 2021			Sanchez-Felipe 2021
Measles	Horner 2020			
VSV	Yaholom-Ronen 2020			
Nanoparticle		Kim 2021		Brouwer 2021
Subunit			Liang 2021, Yang 2020	Guebre-Xavier 2020
Inactivated			Gao 2020	

3.1. Syrian hamster model

Syrian hamsters were used to investigate protection against exposure after vaccination with a wide range of vaccine platforms; mRNA vaccine [20], adenovirus [21], measles virus [22], yellow fever virus [23] and VSV [24]. Vaccine was administered to animals via similar routes (intramuscularly, or intraperitoneally), whereas the dose was difficult to compare between different platforms. Three studies used a single dose [21,23,24], while three studies used two doses, one [23], three [22] or four weeks [20] apart. All animals were challenged intranasally, or both intranasally and intratracheally [20], between days 23 and 42 after the last dose of vaccine. However, the dose used for challenge varied markedly, ranging from 10^2 to 5×10^5 median tissue culture infectious dose ($TCID_{50}$) and from 2×10^5 to 5×10^6 plaque forming units (pfu). All studies checked lungs, and sometimes also nasal turbinates. Limited effects were seen after vaccination with MeVvac2-SARS2-S(H) [22], with only a ten-fold reduction in viral titer in both lungs and nasal turbinates. In contrast, strong reductions, both in number of affected animals and in viral titer in those affected, were seen after vaccination with CVnCoV [20], YF-S0 [23], and rVSV-ΔG-spike [24], with a stronger effect in lungs than in nasal turbinates (see Table 2). In the study using Ad26-S.PP [21] a reduction in mortality was observed, and a strong reduction in the percentage of lung area affected by infection. Although for nasal turbinates, vaccination did not seem to impact the number of animals positive for viral RNA, a 1000-fold reduction in viral load was observed after vaccination with rVSV-ΔG-spike [24].

Neutralizing antibody titers were determined with several techniques and geometric mean titers (GMT) ranged from 20 to 800. Results were not compared to human sera but in one study it was observed that GMTs after vaccination were 2.5–7.5 times higher than in convalescent hamsters [23].

3.2. Ferret model

Only one study was performed in ferrets, to investigate protection against challenge after vaccination with three doses of receptor binding domain (RBD) nanoparticles, at days 0, 14 and 28 [25]. The ferrets were challenged with 10^5 $TCID_{50}$. Viral loads were determined in the nose and lungs, with a strong effect in the nose from day 6 after challenge, whereas no vaccinated animals were positive in the lungs, either at day 3 or day 6 after challenge (see Table 3). Both intramuscular and combined intramuscular/intranasal immunization were tested and the combination gave slightly better results than intramuscular vaccination only [25]. Neutralizing antibody titers were determined by microneutralization assay and a GMT of 64 was observed, with little difference between intramuscular or combined intramuscular/intranasal immunization [25].

3.3. Rhesus macaque model

Rhesus macaques were used to investigate protection against exposure after vaccination with a wide range of vaccine platforms; mRNA vaccine [26–28], adenovirus [29–32], subunit vaccine [33,34], and inactivated virus [35]. Vaccine was generally administrated to animals intramuscularly, with one study using intranasal administration [32]. The dose ranged from 0.5 to 100 μg for mRNA, 10^{10} to 10^{11} virus particles for adenovirus, and 20–40 μg for subunit vaccines. Two studies used a single dose [29,30], while seven studies used two doses, one [34], three [28,33] or four weeks [20,26,27,31,32] apart. In most studies animals were challenged both intranasally and intratracheally, whereas in one study animals were challenged intranasally [34], and in one study intratracheally [29]. Animals were challenged between days 14 and 56 after the last dose of vaccine. However, the dose used for challenge varied strongly, ranging from 2×10^4 to 2.6×10^6 $TCID_{50}$ and from 5×10^5 to 5×10^6 pfu.

Samples obtained included brocheoalveolar lavage (BAL), nasal,

Table 2
Syrian golden hamster model.

First author	Vaccine name	DPI, RNA*	viral load control	positive controls	viral load vaccinated	positive vaccinated
Lung						
Hörner C.	MeVvac2-SARS2-S(H)	4, RNA	6.3×10^9	6 out of 6	3.2×10^8	6 out of 6
Hörner C.	MeVvac2-SARS2-S(H)	4, ti	3.2×10^5	6 out of 6		1 out of 6
Rauch S.	CvnCoV, low	RNA		5 out of 5		4 out of 5
Rauch S.	CvnCoV, high	RNA		5 out of 5		0 out of 5
Sanchez-Felipe L.	YF-S0, 1 dose, low		5×10^5	12 out of 12	6.3×10^1	4 out of 12
Sanchez-Felipe L.	YF-S0, 1 dose, high		5×10^5	12 out of 12		0 out of 12
Sanchez-Felipe L.	YF-S0, 2 dose		4×10^5	12 out of 12		3 out of 12
Yahalom-Ronen Y.	rVSV-ΔG-spike, 10^6	3, RNA	5.6×10^6	4 out of 4	7.3×10^3	2 out of 4
Yahalom-Ronen Y.	rVSV-ΔG-spike, 10^4	5, RNA	10^5	7 out of 7		0 out of 3
Yahalom-Ronen Y.	rVSV-ΔG-spike, 10^5	5, RNA	10^5	7 out of 7		0 out of 3
Yahalom-Ronen Y.	rVSV-ΔG-spike, 10^6	5, RNA	10^5	7 out of 7		0 out of 3
Yahalom-Ronen Y.	rVSV-ΔG-spike, 10^7	5, RNA	10^5	7 out of 7		0 out of 3
Yahalom-Ronen Y.	rVSV-ΔG-spike, 10^8	5, RNA	10^5	7 out of 7		0 out of 3
Lung, affected tissue						
Rauch S.	CvnCoV, low			5 out of 5		2 out of 5
Rauch S.	CvnCoV, high			5 out of 5		0 out of 5
Tostanoski L.	Ad26-S.PP		14%	5 out of 5	0%	1 out of 6
Nasal turbinates						
Hörner C.	MeVvac2-SARS2-S(H)	4, RNA	2×10^{10}	6 out of 6	2×10^9	6 out of 6
Hörner C.	MeVvac2-SARS2-S(H)	4, ti	3.2×10^5	6 out of 6	10^4	5 out of 6
Rauch S.	CvnCoV, low	RNA		5 out of 5		5 out of 5
Rauch S.	CvnCoV, high	RNA		5 out of 5		4 out of 5
Yahalom-Ronen Y.	rVSV-ΔG-spike, 10^6	3, RNA	1.9×10^5	4 out of 4	2.8×10^2	3 out of 4

DPI – days post infection; * RNA – total RNA; sg – subgenomic RNA; ti – virus titration.

Table 3
Ferret animal model.

First author	Vaccine	DPI, RNA*	Positive controls	Positive vaccinated
Nose				
Kim Y. I.	RBD-np	2, RNA	10 out of 10	20 out of 20
Kim Y. I.	RBD-np	4, RNA	7 out of 7	6 out of 14
Kim Y. I.	RBD-np	6, RNA	7 out of 7	0 out of 14
Kim Y. I.	RBD-np	8, RNA	2 out of 4	0 out of 8
Kim Y. I.	RBD-np	10, RNA	0 out of 4	0 out of 8
Lung				
Kim Y. I.	RBD-np	3, RNA	3 out of 3	0 out of 6
Kim Y. I.	RBD-np	6, RNA	3 out of 3	0 out of 6

DPI – days post infection; * RNA – total RNA; sg – subgenomic RNA.

throat and tracheal swabs, and lung tissue. Limited effects on sgRNA in BAL were seen after vaccination with CVnCoV [27], whereas strong reductions in number of sgRNA positive animals were observed after vaccination with mRNA-1273 [26], Ad26-S.PP [30], ChAdOx1 nCoV-19 [31,32], and BNT162b2 [28]. Similarly, strong reductions were seen in lung, nasal swab, throat swab and tracheal swab (Table 4).

Neutralizing antibody titers were determined with several techniques and GMTs ranged from 5 to 27000, with higher doses resulting in higher GMTs [26,27,29], two doses giving higher GMTs than one dose [31], and AS03 adjuvant giving higher GMTs than CpG [33]. Results were compared to human convalescent sera and the GMT ratio ranged from 1 [32,35] to 84 [26].

3.4. Cynomolgus macaque model

Cynomolgus macaques were used to investigate protection against exposure after vaccination with several vaccine platforms; nanoparticle [36], subunit vaccine [37], and yellow fever virus [23]. Vaccine was administrated to animals intramuscularly [36,37], or subcutaneously [23]. Two studies used two doses, one [23], or three weeks [37] apart, while one study used three doses at zero, four and ten weeks [36]. Animals were challenged between days 14 and 21 after the last dose of vaccine. However, the dose used for challenge varied strongly, ranging from 1.04×10^4 to 10^6 pfu, or 100-fold.

Samples obtained included BAL, nasal, throat and tracheal swabs. Strong reductions in number of sgRNA positive BAL samples were observed after vaccination with SARS-CoV-2 S–I53–50NP [36], and NVX-CoV2373 [37]. Similarly, strong reductions were seen in nasal swabs [36,37], and to a lesser degree in throat swabs [23] and tracheal swabs [36] (see Table 5).

Neutralizing antibody titers ranged from 398 to 26000. Results were compared to human convalescent sera and the GMT ratio ranged from 3 [36] to 10 [37].

4. Discussion

In this study we found 18 papers on eight different vaccine platforms in four animal models. All vaccines show a general tendency of impact on virus reduction after infection. While the list of vaccines is not exhaustive, as results with other vaccines will become available, the published data indicate that vaccine challenge trials in non-human primates, ferrets and hamsters show the potential of COVID-19 vaccines to limit or prevent disease and transmission of the virus. A strong reduction of viral load in lungs would demonstrate impact of the vaccine on disease (presence of clinical signs, need for hospitalization, and ICU). Hence, the reduction or prevention of virus replication in the bronchoalveolar environment, consistently shown in animal models, might be related with disease prevention and might explain the high efficacy in clinical trials [38–40]. On the other hand, a strong reduction in excretion would demonstrate the potential of the vaccine to decrease the spread and transmission of SARS-CoV-2. Particularly nasal swab results are likely to give an indication about the impact of virus excretion in the environment. Interestingly, in the non-human primate models, the impact of the vaccine seems to be larger in the lung than in the nose, whereas in the hamster, a model with more severe clinical signs in non-treated animals, the impact of the vaccine in the lung and in the nose seems to be equal although the data with relation to viral presence in the nasal turbinates of hamsters is limited and needs further exploration. Nevertheless, all data taken together, it means that the hamster is a useful model to study vaccine efficacy and may ethically be more acceptable than the use of non-human primates.

If a correlation between results in animal models and results in human populations could be established, standardized animal models might become a way to advance more quickly to gather efficacy data on

Table 4
Rhesus macaque animal model.

First author	Vaccine	DPI, RNA*	control viral load	controls positive	vaccinated viral load	vaccinated positive
BAL						
Corbett K. S.	mRNA-1273	2, sg		8 out of 8		1 out of 8
Corbett K. S.	mRNA-1273	4, sg		4 out of 8		0 out of 8
Corbett K. S.	mRNA-1273	7, sg		1 out of 8		0 out of 8
Mercado N. B.	Ad26-S.PP	sg	7.9×10^4	20 out of 20	0	0 out of 6
van Doremalen N.[a]	ChAdOx1, 1 dose	5, sg		5 out of 6		0 out of 6
van Doremalen N.[a]	ChAdOx1, 2 dose	5, sg		4 out of 6		0 out of 6
van Doremalen N.[b]	ChAdOx1 nCoV-19	sg		4 out of 4		1 out of 4
Vogel A. B.	BNT162b2	3, RNA	10^6	2 out of 3	0	0 out of 6
Vogel A. B.	BNT162b2	6, RNA	5×10^3	1 out of 3	0	0 out of 6
Rauch S.	CvnCoV, live	sg		1 out of 6		0 out of 6
Rauch S.	CvnCoV, pm	sg		1 out of 6		1 out of 6
Lung						
Feng L.	Ad5-S-nb2	RNA		4 out of 4		0 out of 9
Liang J. G.	S-Trimer + AS03	5, RNA		21 out of 32		0 out of 32
Liang J. G.	S-Trimer + CpG	7, RNA		21 out of 32		0 out of 32
Yang J.	RBD - 20ug	7, sg		11 out of 35		0 out of 3
Yang J.	RBD - 40 ug	7, sg		11 out of 35		0 out of 4
van Doremalen N.[a]	ChAdOx1, 2 dose	sg		17 out of 36		2 out of 36
Nasal swab						
Corbett K. S.	mRNA-1273	1, sg		6 out of 8		3 out of 8
Corbett K. S.	mRNA-1273	2, sg		6 out of 8		0 out of 8
Corbett K. S.	mRNA-1273	4, sg		4 out of 8		1 out of 8
Corbett K. S.	mRNA-1273	7, sg		0 out of 8		0 out of 8
Rauch S.	CVnCoV	sg	3.7×10^4	5 out of 6	4×10^3	3 out of 6
Vogel A. B.	BNT162b2	1, RNA	9×10^3	2 out of 3	10^5	5 out of 6
Vogel A. B.	BNT162b2	3, RNA	1.1×10^4	2 out of 3	0	0 out of 6
Vogel A. B.	BNT162b2	6, RNA	2×10^3	1 out of 3	0	0 out of 6
Liang J. G.	S-Trimer + AS03	1, RNA		6 out of 6		5 out of 6
Liang J. G.	S-Trimer + CpG	1, RNA		6 out of 6		6 out of 6
Liang J. G.	S-Trimer + AS03	3, RNA		4 out of 6		4 out of 6
Liang J. G.	S-Trimer + CpG	3, RNA		4 out of 6		4 out of 6
Liang J. G.	S-Trimer + AS03	5, RNA		2 out of 6		4 out of 6
Liang J. G.	S-Trimer + CpG	5, RNA		2 out of 6		1 out of 6
Liang J. G.	S-Trimer + AS03	7, RNA		1 out of 6		1 out of 6
Liang J. G.	S-Trimer + CpG	7, RNA		1 out of 6		1 out of 6
Mercado N. B.	Ad26-S.PP	sg	2.5×10^5	20 out of 20	0	1 out of 6
van Doremalen N.[a]	ChAdOx1, 1 dose	0, sg		1 out of 6		2 out of 6
van Doremalen N.[a]	ChAdOx1, 1 dose	3, sg		4 out of 6		4 out of 6
van Doremalen N.[a]	ChAdOx1, 1 dose	5, sg		0 out of 6		1 out of 6
van Doremalen N.[a]	ChAdOx1, 1 dose	7, sg		0 out of 6		0 out of 6
van Doremalen N.[a]	ChAdOx1, 2 dose	0, sg		1 out of 6		3 out of 6
van Doremalen N.[a]	ChAdOx1, 2 dose	3, sg		4 out of 6		2 out of 6
van Doremalen N.[a]	ChAdOx1, 2 dose	5, sg		0 out of 6		2 out of 6
van Doremalen N.[a]	ChAdOx1, 2 dose	7, sg		0 out of 6		0 out of 6
van Doremalen N.[b]	ChAdOx1 nCoV-19	sg		3 out of 4		1 out of 4
Throat						
Vogel A. B.	BNT162b2	1, RNA	7.5×10^4	3 out of 3	1.2×10^3	3 out of 6
Vogel A. B.	BNT162b2	3, RNA	1.3×10^4	3 out of 3	1.1×10^3	2 out of 6
Vogel A. B.	BNT162b2	10, RNA	10^3	1 out of 3	10^3	1 out of 6
Feng L.	Ad5-S-nb2	AUC	1.3×10^6		5×10^2	
Feng L.	Ad5-S-nb2	7, RNA		5 out of 6		4 out of 9
Liang J. G.	S-Trimer + AS03	1, RNA		5 out of 6		1 out of 6
Liang J. G.	S-Trimer + CpG	1, RNA		5 out of 6		3 out of 6
Liang J. G.	S-Trimer + AS03	3, RNA		4 out of 6		1 out of 6
Liang J. G.	S-Trimer + CpG	3, RNA		4 out of 6		0 out of 6
Liang J. G.	S-Trimer + AS03	5, RNA		2 out of 6		1 out of 6
Liang J. G.	S-Trimer + CpG	5, RNA		2 out of 6		0 out of 6
Liang J. G.	S-Trimer + AS03	7, RNA		1 out of 6		0 out of 6
Liang J. G.	S-Trimer + CpG	7, RNA		1 out of 6		1 out of 6
Yang J.	RBD - 20ug	3, sg		5 out of 5		0 out of 3
Yang J.	RBD - 40 ug	3, sg		5 out of 5		0 out of 4
Yang J.	RBD - 20ug	4, sg		5 out of 5		0 out of 3
Yang J.	RBD - 40 ug	4, sg		5 out of 5		0 out of 4
Yang J.	RBD - 20ug	5, sg		3 out of 5		0 out of 3
Yang J.	RBD - 40 ug	5, sg		3 out of 5		0 out of 4
Yang J.	RBD - 20ug	6, sg		5 out of 5		0 out of 3
Yang J.	RBD - 40 ug	6, sg		5 out of 5		0 out of 4
Tracheal swab						
Liang J. G.	S-Trimer + AS03	1, RNA		6 out of 6		6 out of 6
Liang J. G.	S-Trimer + CpG	1, RNA		6 out of 6		3 out of 6
Liang J. G.	S-Trimer + AS03	3, RNA		5 out of 6		1 out of 6
Liang J. G.	S-Trimer + CpG	3, RNA		5 out of 6		1 out of 6

(*continued on next page*)

Table 4 (*continued*)

First author	Vaccine	DPI, RNA*	control viral load	controls positive	vaccinated viral load	vaccinated positive
Liang J. G.	S-Trimer + AS03	5, RNA		1 out of 6		0 out of 6
Liang J. G.	S-Trimer + CpG	5, RNA		1 out of 6		0 out of 6
Liang J. G.	S-Trimer + AS03	7, RNA		0 out of 6		1 out of 6
Liang J. G.	S-Trimer + CpG	7, RNA		0 out of 6		2 out of 6

AUC – area under the curve; BAL – broncho-alveolar lavage; dpi – days post infection; pm – post mortem; * RNA – total RNA; sg – subgenomic RNA.

Table 5
Cynomolgus macaque.

First author	Vaccine	DPI, RNA*	Control viral load	Controls positive	Vaccinated viral load	Vaccinated positive
BAL						
Brouwer P. J. M.	SARS-CoV-2 S–I53–50NP	3, RNA	2.3×10^4	4 out of 4	3.2×10^2	0 out of 6
Guebre-Xabier M.	NVX-CoV2373-low	2, sg	7.9×10^3	4 out of 4		1 out of 4
Guebre-Xabier M.	NVX-CoV2373-low	4, sg	4×10^2	3 out of 4		0 out of 4
Guebre-Xabier M.	NVX-CoV2373-medium	2, sg	8×10^3	4 out of 4		0 out of 4
Guebre-Xabier M.	NVX-CoV2373-medium	4, sg	4×10^2	3 out of 4		0 out of 4
Guebre-Xabier M.	NVX-CoV2373-high	2, sg	8×10^3	4 out of 4		0 out of 4
Guebre-Xabier M.	NVX-CoV2373-high	4, sg	4×10^2	3 out of 4		0 out of 4
Nasal swab						
Guebre-Xabier M.	NVX-CoV2373-low	2, sg		1 out of 4		0 out of 4
Guebre-Xabier M.	NVX-CoV2373-low	4, sg		2 out of 4		0 out of 4
Guebre-Xabier M.	NVX-CoV2373-medium	2, sg		1 out of 4		0 out of 4
Guebre-Xabier M.	NVX-CoV2373-medium	4, sg		2 out of 4		0 out of 4
Guebre-Xabier M.	NVX-CoV2373-high	2, sg		1 out of 4		0 out of 4
Guebre-Xabier M.	NVX-CoV2373-high	4, sg		2 out of 4		0 out of 4
Brouwer P. J. M.	SARS-CoV-2 S–I53–50NP	2, RNA	1.6×10^6	4 out of 4	3.2×10^2	0 out of 6
Brouwer P. J. M.	SARS-CoV-2 S–I53–50NP	5, RNA		3 out of 4		0 out of 6
Brouwer P. J. M.	SARS-CoV-2 S–I53–50NP	6, RNA		2 out of 4		0 out of 6
Throat						
Sanchez-Felipe L.	YF-S0	1, RNA		2 out of 6		0 out of 6
Sanchez-Felipe L.	YF-S0	2, RNA		3 out of 6		1 out of 6
Sanchez-Felipe L.	YF-S0	3, RNA		1 out of 6		0 out of 6
Sanchez-Felipe L.	YF-S0	4, RNA		1 out of 6		0 out of 6
Trachea						
Brouwer P. J. M.	SARS-CoV-2 S–I53–50NP	2, RNA	5×10^4	4 out of 4	3.2×10^2	2 out of 6
Brouwer P. J. M.	SARS-CoV-2 S–I53–50NP	5, RNA		1 out of 4		0 out of 6
Brouwer P. J. M.	SARS-CoV-2 S–I53–50NP	6, RNA		0 out of 4		0 out of 6

BAL – broncho-alveolar lavage; DPI – days post infection; * RNA – total RNA; sg – subgenomic RNA.

SARS-CoV-2 vaccines.

For instance, the study by Mercado et al. [30] shows an inverse correlation between the antibody titer and virus recovery, which is likely the same for all vaccines. Since neutralizing antibodies are relatively easy to determine, if this biomarker proves reliable, it would be an important tool to speed up vaccine development against COVID-19, in association with vaccine challenge results in animal models.

Transmission of SARS-CoV-2 between animals has been observed, both in animal models [41,42] and in farm animals [43]. Vaccine-challenge trials have been performed for a number of infectious agents (mostly viral, occasionally bacterial) in a range of animal species [44–47]. Regrettably, to our knowledge, no vaccine-challenge trials have been performed so far for SARS-CoV-2, which could have shed light on the impact of vaccination on contact and airborne transmission of SARS-CoV-2.

Our review has brought to light several limitations. First, the challenge dose varied strongly between experiments, not only between animal models but also within animal models. Therefore, we limited the comparison to general tendencies, because animal experiments show variability according to challenge administration route and species [48]. Finally, a number of manuscripts covered in this review were published on preprint servers, and have not yet undergone peer review, these studies should therefore be interpreted with caution. Moreover, these studies are often (co-)published by employees of the vaccine manufacturer, who inherently have a conflict of interest, further demanding caution in interpretation of the data.

The findings in animal models have now been confirmed by field evidence, particularly in countries where the vaccination coverage is already substantial. In Israel, with more than 60% of the population vaccinated with the Pfizer/BioNTech vaccine, vaccination results in a positive effect on the reduction of new infections rates, with a 85% reduction in the symptomatic group and 75% for all SARS-CoV-2 positive cases at 15–28 days after the first dose [7]. A comparable trend has been observed in the UK, where a significant reduction of symptomatic and asymptomatic infections was seen in working age adults [49]. Further observations based on data from 1,14 million vaccinations in Scotland showed that both Pfizer/BioNtech and AstraZeneca vaccines are highly effective and reduce the risk of hospitalization from COVID-19 by up to 85% and 94%, respectively, four weeks after the first dose [50]. In addition, people aged 80 years or more, vaccinated with either vaccine showed an 81% reduction in hospitalization [50]. Recent data also directly showed that transmission is reduced from vaccinated people to their family members [8,9].

In conclusion, all SARS-CoV-2 vaccine candidates in this review, based on various vaccine platforms and different immunogens, reduce – after exposure - viral load in different organs in animal models. It remains difficult to compare the results obtained with vaccines directly, since the animal models and the exposure conditions vary. However, even if the data on viral shedding are scarce or not fully reliable in the animal models, a strong effect on the reduction of transmission is shown. Hence, the animal models predicted what is observed in the field after large scale vaccination of human populations. These interesting results merit further attention for standardization of exposure experiments to estimate more precisely the impact of each vaccine on the circulation of

wild virus in the population, with the intention to speed up future vaccine development.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.biologicals.2021.08.001.

References

[1] Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature 2020;579:265–9.

[2] Karpiński TM, Ożarowski M, Seremak-Mrozikiewicz A, Wolski H, Wlodkowic D. The 2020 race towards SARS-CoV-2 specific vaccines. Theranostics 2021;11:1690–702.

[3] World Health Organization, CEPI. GAVI the vaccine alliance. Workshop on "pre- and post- licensure assessments of COVID- 19 vaccine efficacy/effectiveness against infection & transmission" co-organised by the COVAX clinical development & operations SWAT team and the COVAX post introduction evaluations workstream. Available from: https://media.tghn.org/medialibrary/2021/01/COVAX_Transmission_Workshop_REPORT_FINAL_MPJGAyT.pdf.

[4] European Medicines Agency. COVID-19 vaccines: Authorised. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised#authorised-covid-19-vaccines-section. [Accessed 25 March 2021].

[5] Us Food & Drug Administration. COVID-19 vaccines. Available from: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines. [Accessed 25 March 2021].

[6] Levine-Tiefenbrun M, Yelin I, Katz R, Herzel E, Golan Z, Schreiber L, et al. Decreased SARS-CoV-2 viral load following vaccination. medRxiv 2021. https://doi.org/10.1101/2021.02.06.21251283.

[7] Amit S, Regev-Yochay G, Afek A, Kreiss Y, Leshem E. Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients. Lancet 2021;397:875–7.

[8] Shah AS, Gribben C, Bishop J, Hanlon P, Caldwell D, Wood R, et al. Effect of vaccination on transmission of COVID-19: an observational study in healthcare workers and their households. medRxiv 2021. https://doi.org/10.1101/2021.03.11.21253275.

[9] Harris R, Hall J, Zaidi A, Andrews N, Dunbar K, Dabrera G. Impact of vaccination on household transmission of SARS-COV-2 in England. Available from: https://khub.net/documents/135939561/390853656/Impact+of+vaccination+on+household+transmission+of+SARS-COV-2+in+England.pdf/35bf4bb1-6ade-d3eb-a39e-9c9b25a8122a?t=1619601878136.

[10] Munster VJ, Feldmann F, Williamson BN, van Doremalen N, Pérez-Pérez L, Schulz J, et al. Respiratory disease in rhesus macaques inoculated with SARS-CoV-2. Nature 2020;585:268–72.

[11] Salguero FJ, White AD, Slack GS, Fotheringham SA, Bewley KR, Gooch KE, et al. Comparison of rhesus and cynomolgus macaques as an infection model for COVID-19. Nat Commun 2021;12:1260.

[12] Ishigaki H, Nakayama M, Kitagawa Y, Nguyen CT, Hayashi K, Shiohara M, et al. Neutralizing antibody-dependent and -independent immune responses against SARS-CoV-2 in cynomolgus macaques. Virology 2021;554:97–105.

[13] Kim YI, Kim SG, Kim SM, Kim EH, Park SJ, Yu KM, et al. Infection and rapid transmission of SARS-CoV-2 in ferrets. Cell Host Microbe 2020;27:704. 9.e2.

[14] Imai M, Iwatsuki-Horimoto K, Hatta M, Loeber S, Halfmann PJ, Nakajima N, et al. Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development. Proc Natl Acad Sci U S A 2020;117:16587–95.

[15] Heegaard PMH, Sturek M, Alloosh M, Belsham GJ. Animal models for COVID-19: more to the picture than ACE2, rodents, ferrets, and non-human primates. A case for porcine respiratory coronavirus and the obese ossabaw pig. Front Microbiol 2020;11:573756.

[16] Ehaideb SN, Abdullah ML, Abuyassin B, Bouchama A. Evidence of a wide gap between COVID-19 in humans and animal models: a systematic review. Crit Care 2020;24:594.

[17] Hewitt JA, Lutz C, Florence WC, Pitt MLM, Rao S, Rappaport J, et al. ACTIVating resources for the COVID-19 pandemic: in vivo models for vaccines and therapeutics. Cell Host Microbe 2020;28:646–59.

[18] Muñoz-Fontela C, Dowling WE, Funnell SGP, Gsell PS, Riveros-Balta AX, Albrecht RA, et al. Animal models for COVID-19. Nature 2020;586:509–15.

[19] Woolsey C, Borisevich V, Prasad AN, Agans KN, Deer DJ, Dobias NS, et al. Establishment of an African green monkey model for COVID-19 and protection against re-infection. Nat Immunol 2021;22:86–98.

[20] Rauch S, Roth N, Schwendt K, Fotin-Mleczek M, Mueller SO, Petsch B. mRNA based SARS-CoV-2 vaccine candidate CVnCoV induces high levels of virus neutralizing antibodies and mediates protection in rodents. bioRxiv 2021. https://doi.org/10.1101/2020.10.23.351775.

[21] Tostanoski LH, Wegmann F, Martinot AJ, Loos C, McMahan K, Mercado NB, et al. Ad26 vaccine protects against SARS-CoV-2 severe clinical disease in hamsters. Nat Med 2020;26:1694–700.

[22] Hörner C, Schürmann C, Auste A, Ebenig A, Muraleedharan S, Dinnon 3rd KH, et al. A highly immunogenic and effective measles virus-based Th1-biased COVID-19 vaccine. Proc Natl Acad Sci U S A 2020;117:32657–66.

[23] Sanchez-Felipe L, Vercruysse T, Sharma S, Ma J, Lemmens V, Van Looveren D, et al. A single-dose live-attenuated YF17D-vectored SARS-CoV-2 vaccine candidate. Nature 2021;590:320–5. https://doi.org/10.1038/s41586-020-3035-9.

[24] Yahalom-Ronen Y, Tamir H, Melamed S, Politi B, Shifman O, Achdout H, et al. A single dose of recombinant VSV-ΔG-spike vaccine provides protection against SARS-CoV-2 challenge. Nat Commun 2020;11:6402.

[25] Kim YI, Kim D, Yu KM, Seo HD, Lee SA, Casel MAB, et al. Development of spike receptor-binding domain nanoparticles as a vaccine candidate against SARS-CoV-2 infection in ferrets. mBio 2021;12.

[26] Corbett KS, Flynn B, Foulds KE, Francica JR, Boyoglu-Barnum S, Werner AP, et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. N Engl J Med 2020;383:1544–55.

[27] Rauch S, Gooch K, Hall Y, Salguero FJ, Dennis MJ, Gleeson FV, et al. mRNA vaccine CVnCoV protects non-human primates from SARS-CoV-2 challenge infection. bioRxiv 2020. https://doi.org/10.1101/2020.12.23.424138.

[28] Vogel AB, Kanevsky I, Che Y, Swanson KA, Muik A, Vormehr M, et al. A prefusion SARS-CoV-2 spike RNA vaccine is highly immunogenic and prevents lung infection in non-human primates. bioRxiv 2020. https://doi.org/10.1101/2020.09.08.280818.

[29] Feng L, Wang Q, Shan C, Yang C, Feng Y, Wu J, et al. An adenovirus-vectored COVID-19 vaccine confers protection from SARS-COV-2 challenge in rhesus macaques. Nat Commun 2020;11:4207.

[30] Mercado NB, Zahn R, Wegmann F, Loos C, Chandrashekar A, Yu J, et al. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. Nature 2020;586:583–8.

[31] van Doremalen N, Lambe T, Spencer A, Belij-Rammerstorfer S, Purushotham JN, Port JR, et al. ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques. Nature 2020;586:578–82.

[32] van Doremalen N, Purushotham J, Schulz J, Holbrook M, Bushmaker T, Carmody A, et al. Intranasal ChAdOx1 nCoV-19/AZD1222 vaccination reduces shedding of SARS-CoV-2 D614G in rhesus macaques. bioRxiv 2021. https://doi.org/10.1101/2021.01.09.426058.

[33] Liang JG, Su D, Song TZ, Zeng Y, Huang W, Wu J, et al. S-Trimer, a COVID-19 subunit vaccine candidate, induces protective immunity in nonhuman primates. Nat Commun 2021;12:1346.

[34] Yang J, Wang W, Chen Z, Lu S, Yang F, Bi Z, et al. A vaccine targeting the RBD of the S protein of SARS-CoV-2 induces protective immunity. Nature 2020;586:572–7.

[35] Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science 2020;369:77–81.

[36] Brouwer PJM, Brinkkemper M, Maisonnasse P, Dereuddre-Bosquet N, Grobben M, Claireaux M, et al. Two-component spike nanoparticle vaccine protects macaques from SARS-CoV-2 infection. Cell 2021;184:1188–200. e19.

[37] Guebre-Xabier M, Patel N, Tian J-H, Zhou B, Maciejewski S, Lam K, et al. NVX-CoV2373 vaccine protects cynomolgus macaque upper and lower airways against SARS-CoV-2 challenge. Vaccine 2020;38(50). https://doi.org/10.1016/j.vaccine.2020.10.064.

[38] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403–16.

[39] Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397:99–111.

[40] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. N Engl J Med 2020;383:2603–15.

[41] Chan JF, Zhang AJ, Yuan S, Poon VK, Chan CC, Lee AC, et al. Simulation of the clinical and pathological manifestations of coronavirus disease 2019 (COVID-19) in a golden Syrian hamster model: implications for disease pathogenesis and transmissibility. Clin Infect Dis 2020;71:2428–46.

[42] Sia SF, Yan LM, Chin AWH, Fung K, Choy KT, Wong AYL, et al. Pathogenesis and transmission of SARS-CoV-2 in golden hamsters. Nature 2020;583:834–8.

[43] Oreshkova N, Molenaar RJ, Vreman S, Harders F, Oude Munnink BB, Hakze-van der Honing RW, et al. SARS-CoV-2 infection in farmed minks, The Netherlands, April and May 2020. Euro Surveill 2020;25.

[44] García A, Romo F, Ortiz AM, Blackall PJ. The vaccination-challenge trial: the gold standard test to evaluate the protective efficacy of infectious coryza vaccines. Avian Pathol 2008;37:183–6.

[45] Hoang P, Gerber PF, Reynolds P, McMillan M, Gray P, Walkden-Brown SW. Preliminary testing in turkeys of the safety and efficacy of a putative haemorrhagic enteritis virus vaccine. Aust Vet J 2019;97:323–32.

[46] Jas D, Frances-Duvert V, Vernes D, Guigal PM, Poulet H. Three-year duration of immunity for feline herpesvirus and calicivirus evaluated in a controlled vaccination-challenge laboratory trial. Vet Microbiol 2015;177:123–31.

[47] Nadeau É, Fairbrother JM, Zentek J, Bélanger L, Tremblay D, Tremblay CL, et al. Efficacy of a single oral dose of a live bivalent E. coli vaccine against post-weaning diarrhea due to F4 and F18-positive enterotoxigenic E. coli. Vet J 2017;226:32–9.

[48] Singh A, Singh RS, Sarma P, Batra G, Joshi R, Kaur H, et al. A comprehensive review of animal models for coronaviruses: SARS-CoV-2, SARS-CoV, and MERS-CoV. Virol Sin 2020;35:290–304.

[49] Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, et al. Effectiveness of BNT162b2 mRNA vaccine against infection and COVID-19 vaccine coverage in healthcare workers in England, multicentre prospective cohort study (the SIREN study). Lancet 2021;397:1725–35. https://doi.org/10.2139/ssrn.3790399.

[50] Vasileiou E, Simpson C, Robertson C, al e. Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland: national prospective cohort study

of 5.4 million people. Available from: https://www.ed.ac.uk/files/atoms/files/scotland_firstvaccinedata_preprint.pdf. [Accessed 31 March 2021].