Covid 19 perspectives thérapeutiques et vaccinales

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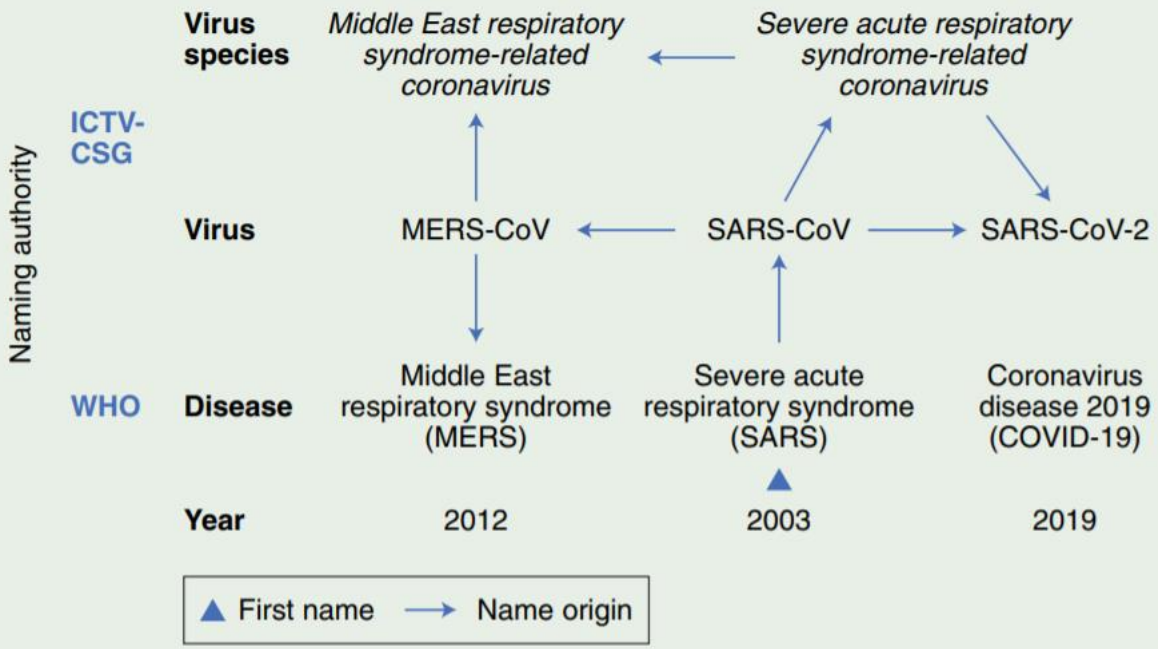


History of coronavirus naming during the three zoonotic outbreaks in relation to virus taxonomy and diseases caused by these viruses. According to the current international classification of diseases[49], MERS and SARS are classified as 1D64 and 1D65, respectively.

Nature Microbiology | VOL 5 | March 2020 | 536–544

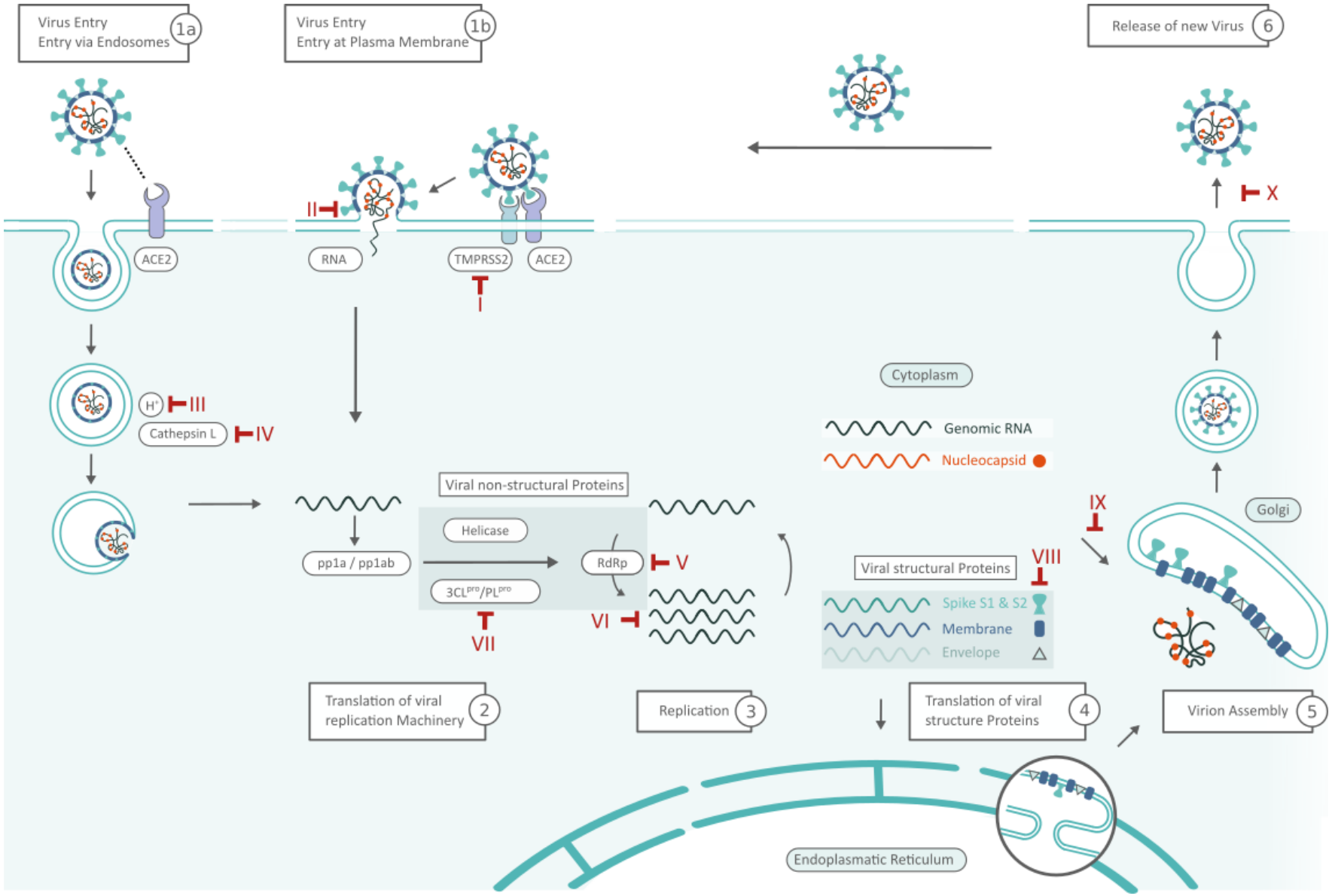

Virus Entry
Entry via Endosomes
1a
Virus Entry
Entry at Plasma Membrane
1b
Release of new Virus
6
ACE2
RNA
TMPRSS2
ACE2
II
I
X
H+
III
Cathepsin L
IV
Cytoplasm
Genomic RNA
Nucleocapsid
Viral non-structural Proteins
Helicase
pp1a / pp1ab
RdRp
V
3CLpro/PLpro
VI
VII
IX
Golgi
Viral structural Proteins
VIII
Spike S1 & S2
Membrane
Envelope
Translation of viral
replication Machinery
2
Replication
3
Translation of viral
structure Proteins
4
Virion Assembly
5
Endoplasmatic Reticulum

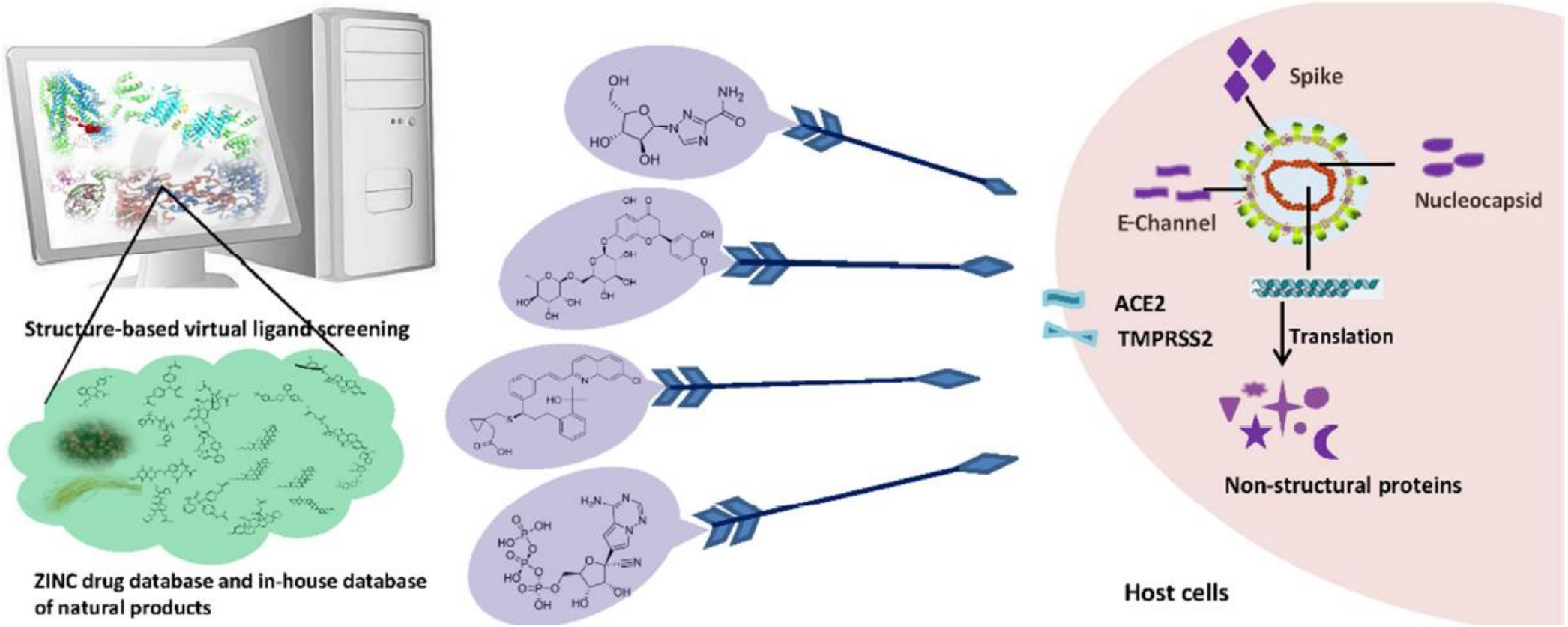
Figure 5. Distribution of patents related to SARS (A) and MERS (B) based on application purpose.

Table 2. Key Proteins and Their Roles during the Viral Infection Process

target candidate	full name	role during viral infection	drug candidate
3CLpro	coronavirus main protease 3CLpro	a protease for the proteolysis of viral polyprotein into functional units	lopinavir[19,30]
PLpro	papain-like protease PLpro	a protease for the proteolysis of viral polyprotein into functional units	lopinavir[19,30]
RdRp	RNA-dependent RNA polymerase	an RNA-dependent RNA polymerase for replicating viral genome	remdesivir,[19,29,32] ribavirin[16,29,31]
S protein	viral spike glycoprotein	a viral surface protein for binding to host cell receptor ACE2	Arbidol[20,22,33a]
TMPRSS2	transmembrane protease, serine 2	a host cell-produced protease that primes S protein to facilitate its binding to ACE2	camostat mesylate[11]
ACE2	angiotensin-converting enzyme 2	a viral receptor protein on the host cells which binds to viral S protein	Arbidol[20,22,33a]
AT2	angiotensin AT2 receptor	an important effector involved in the regulation of blood pressure and volume of the cardiovascular system	L-163491[28]

[a]An inhibitor of viral entry to host cells. Its direct action on S protein and ACE2 is yet to be confirmed.

ACS Cent. Sci. 2020, 6, 315−331



Screening : 78 antivirales

Acta Pharmaceutica Sinica B , doi.org/10.1016/j.apsb.2020.02.008

Table 7. Examples of Similar Molecules with Possible Therapeutic Effects Identified by Structural Similarity, Lipinski's Rule of 5, and Pharmacology/Therapeutic Role Assigned by CAS Scientists during Document Indexing

query substance name (CAS RN)	no. of substances with >60% similarity	example of selected similar substance	Registry Number of selected similar substance
ribavirin (36791-04-5)	1520	viramidine	119567-79-2
galidesivir (249503-25-1)	502	(2*R*,3*S*,5*R*)-5-(4-amino-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)-3-hydroxy-2-pyrrolidinemethanol	1610426-50-0
		(2*S*,4*R*,5*S*)-5-(4-amino-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)-4-hydroxy-2-pyrrolidinemethanol	872534-76-4
		(2*R*,3*R*,4*S*,5*S*)-5-(4-amino-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)-3-hydroxy-4-methoxy-2-pyrrolidinemethanol	1610426-51-1
chloroquine (54-05-7)	21176	hydroxychloroquine	118-42-3
		(±)-chloroquine diphosphate	50-63-5
		chloroquine hydrochloride	3545-67-3
		chloroquine sulfate	132-73-0
favipiravir (259793-96-9)	309	6-bromo-3,4-dihydro-3-oxo-2-pyrazine-5-d-carboxamide	1476773-04-2
		6-fluoro-3,4-dihydro-3-oxo-2-pyrazine-5-d-carboxamide	1492021-26-7
2-butanone, 3-hydroperoxy-4-[2-hydroxy-3-[3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]-6-methoxyphenyl] (2409054-44-8)	63195	xanthoangelol D	132998-83-5

Table 4. Existing Drugs with Therapeutic Potentials for COVID-19 (Drug Repurposing)

drug candidate	CAS RN	target	possible mechanism of action on COVID-19	disease indication
baricitinib[35]	1187594-09-7	JAK kinase	a JAK inhibitor that may interfere with the inflammatory processes	approved drug for rheumatoid arthritis
lopinavir[19a]	192725-17-0	viral proteases: 3CLpro or PLpro	protease inhibitors that may inhibit the viral proteases: 3CLpro or PLpro	lopinavir and ritonavir are approved drug combination for HIV infection
ritonavir[19,37c]	155213-67-5			
darunavir[33]	206361-99-1			approved drug for HIV infection
favipiravir (favilavir)[29,36]	259793-96-9	RdRp	a purine nucleoside that acts as an alternate substrate leading to inaccurate viral RNA synthesis	viral infections
remdesivir[19,29,32a]	1809249-37-3		a nucleotide analogue that may block viral nucleotide synthesis to stop viral replication	Ebola virus infection
ribavirin[16,29−31a]	36791-04-5			RSV infection, hepatitis C, some viral hemorrhagic fevers
galidesivir[34b]	249503-25-1			hepatitis C, Ebola virus, Marburg virus
BCX-4430 (salt form of galidesivir)[34b]	222631-44-9			hepatitis C, Ebola virus, Marburg virus
Arbidol[22,33a]	131707-23-8	S protein/ ACE2[d]	an inhibitor that may disrupt the binding of viral envelope protein to host cells and prevent viral entry to the target cell	influenza antiviral drug
chloroquine[29,32]	54-05-7	endosome/ ACE2	a drug that can elevate endosomal pH and interfere with ACE2 glycosylation	malarial parasite infection
nitazoxanide[29]	55981-09-4	N/A	a drug that may inhibit viral protein expression	various helminthic, protozoal, and viral infection-caused diarrhea

[a]Drugs under clinical trials for treating COVID-19 (repurposing). [b]Drugs under clinical trials for other virus-induced diseases. [c]Ritonavir is a pharmacokinetic profile enhancer that may potentiate the effects of other protease inhibitors due to its ability to attenuate the degradation of those drugs by the liver enzyme CYP3A4 and thus is used in combination with antivirial Lopinavir.[37] [d]An inhibitor of viral entry to host cells. Its direct action on S protein and ACE2 is yet to be confirmed.

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Remdesivir

Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection

Emmie de Wit[a,1], Friederike Feldmann[b], Jacqueline Cronin[a], Robert Jordan[c], Atsushi Okumura[d], Tina Thomas[a], Dana Scott[b], Tomas Cihlar[c], and Heinz Feldmann[a]

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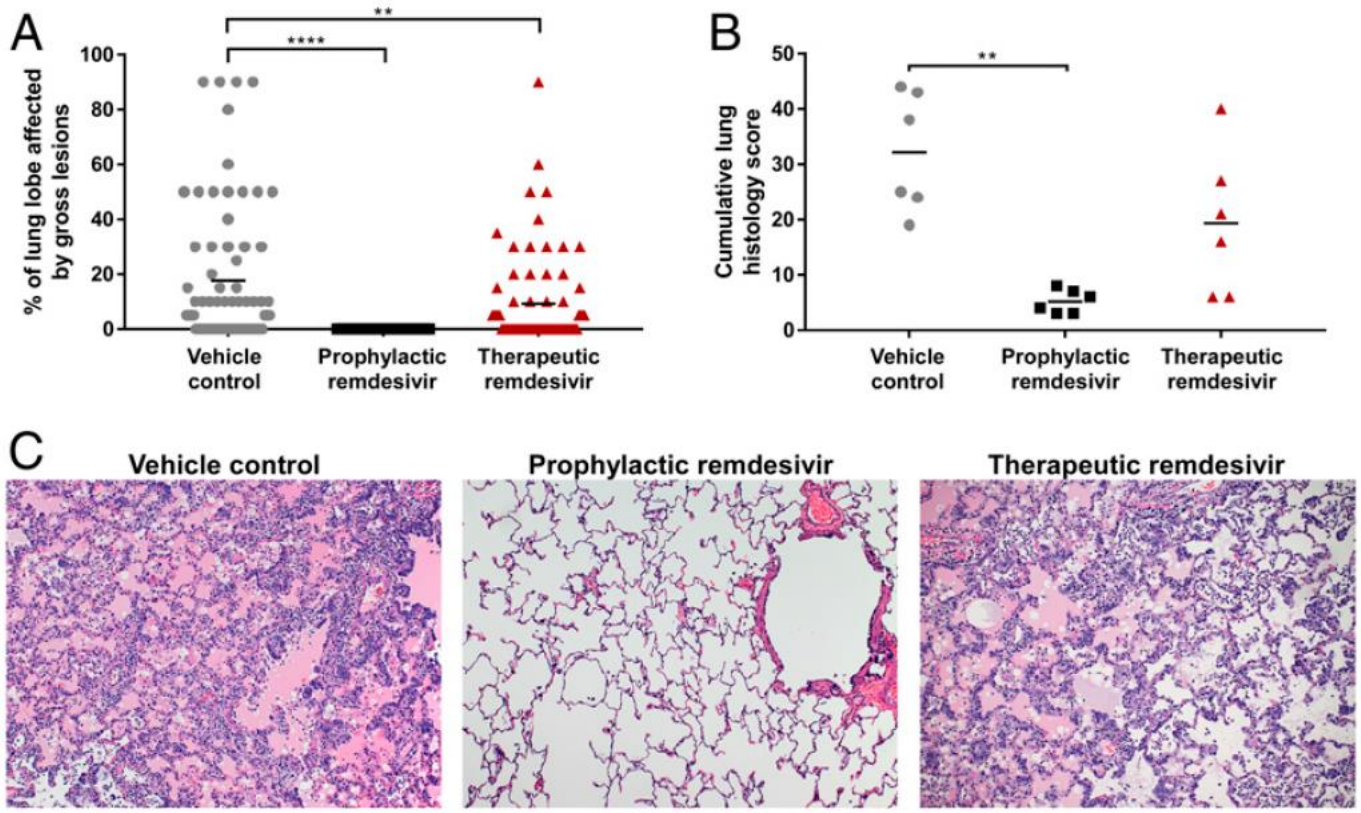

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AMERICAN SOCIETY FOR MICROBIOLOGY | mBio®

March/April 2018 Volume 9 Issue 2 e00221-18

Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease

Maria L. Agostini,[a] Erica L. Andres,[b] Amy C. Sims,[c] Rachel L. Graham,[c] Timothy P. Sheahan,[c] Xiaotao Lu,[b] Everett Clinton Smith,[b,d] James Brett Case,[a] Joy Y. Feng,[e] Robert Jordan,[e] Adrian S. Ray,[e] Tomas Cihlar,[e] Dustin Siegel,[e] Richard L. Mackman,[e] Michael O. Clarke,[e] Ralph S. Baric,[c] Mark R. Denison[a,b]

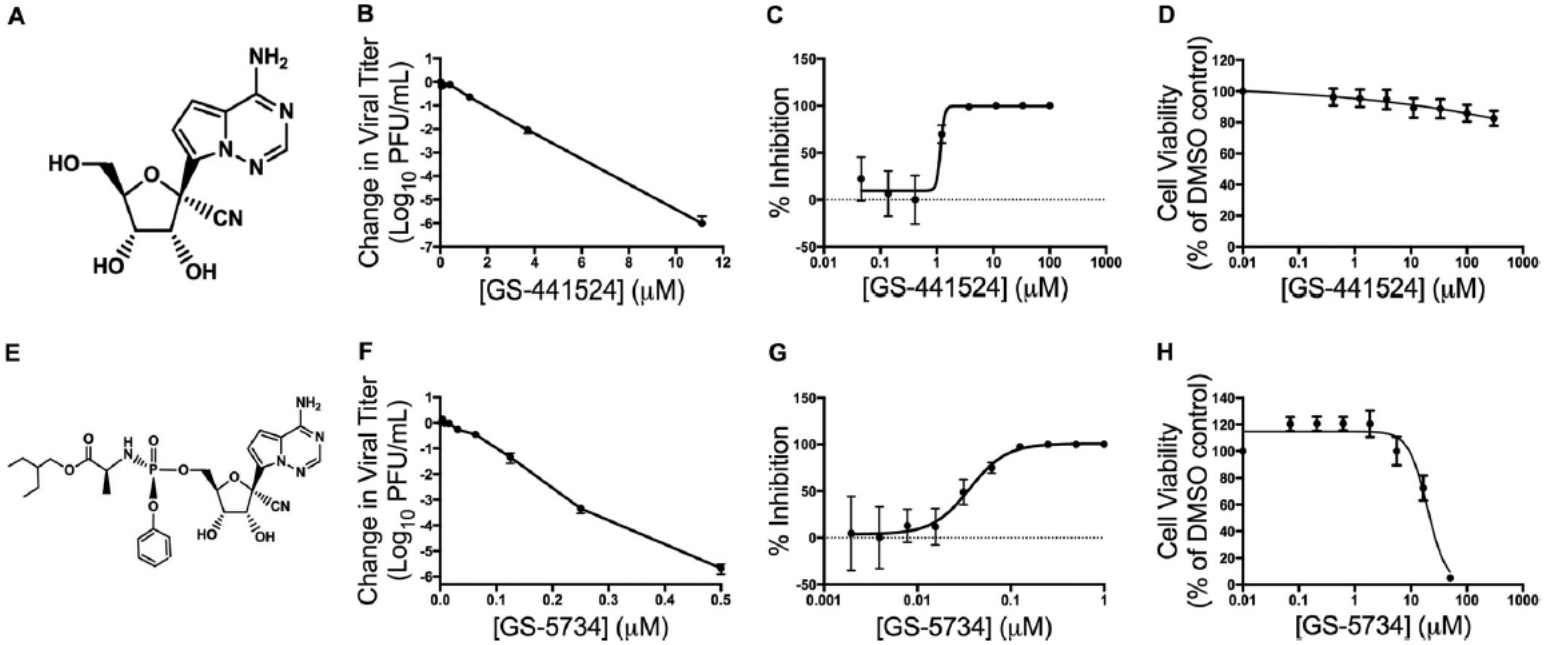


FIG 1 GS-441524 and GS-5734 inhibit MHV with minimal cytotoxicity. (A) GS-441524 is a 1′-cyano 4-aza-7,9-dideazaadenosine C-adenosine nucleoside analogue. (B) Change in viral titer of MHV compared to vehicle control after treatment with GS-441524. The data represent the results from 2 independent experiments, each with 3 replicates. Error bars represent standard error of the mean (SEM). (C) Viral titer data from panel B presented as the percentage of uninhibited control. The EC_{50} of GS-441524 was calculated to be 1.1 μM. (D) Cell viability normalized to the vehicle control after treatment with GS-441524. The data represent the results from 3 independent experiments, each with 3 replicates. Error bars represent SEM. (E) GS-5734 is a monophosphoramidate prodrug of GS-441524. (F) Change in viral titer of MHV compared to vehicle control after treatment with GS-5734. The data represent the results from 4 independent experiments, each with 3 replicates. Error bars represent SEM. (G) Viral titer data from panel F presented as the percentage of uninhibited control. The EC_{50} of GS-5734 was calculated to be 0.03 μM. (H) Cell viability normalized to vehicle control after treatment with GS-5734. The data represent the results from 3 independent experiments, each with 3 replicates. Error bars represent SEM.

https://doi.org/10.1038/s41467-019-13940-6

Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV

Timothy P. Sheahan[1,5*], Amy C. Sims[1,5], Sarah R. Leist[1], Alexandra Schäfer[1], John Won[1], Ariane J. Brown[1],

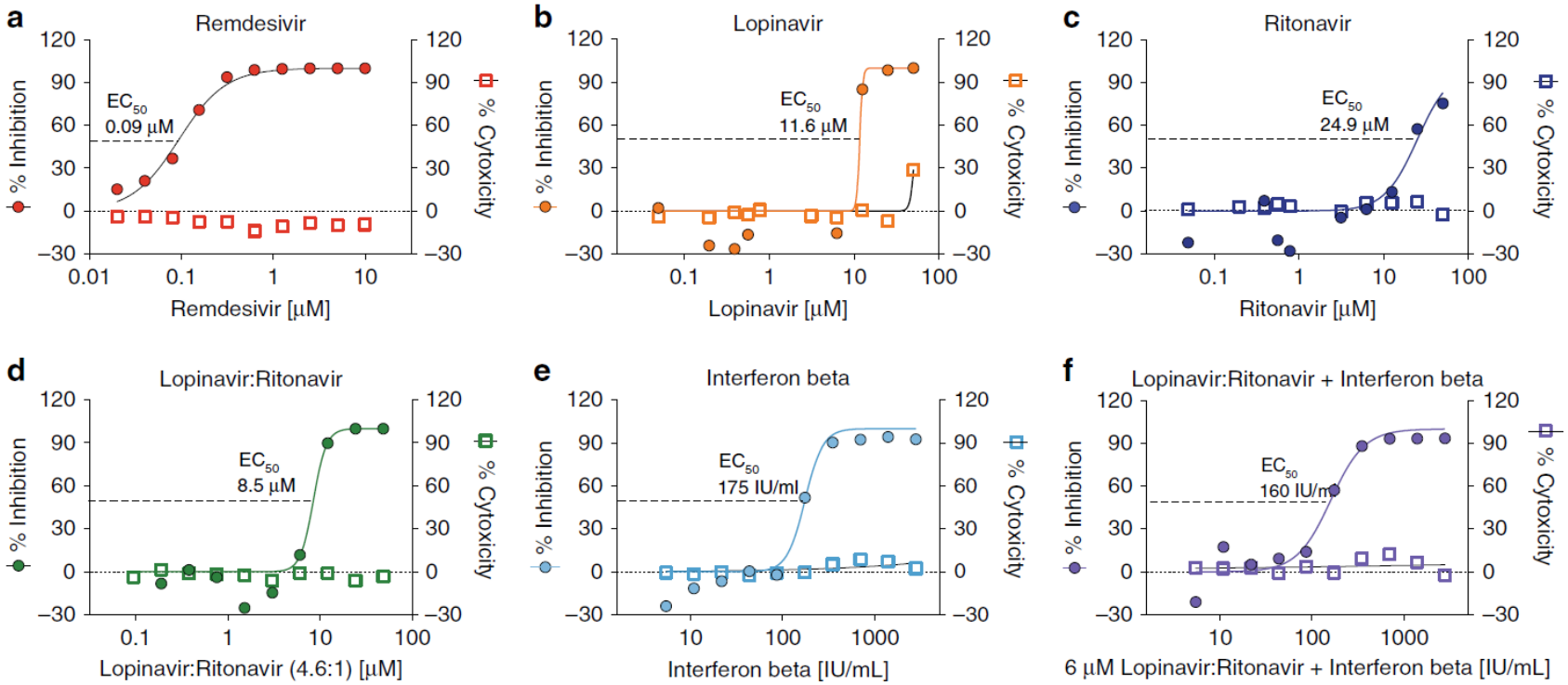
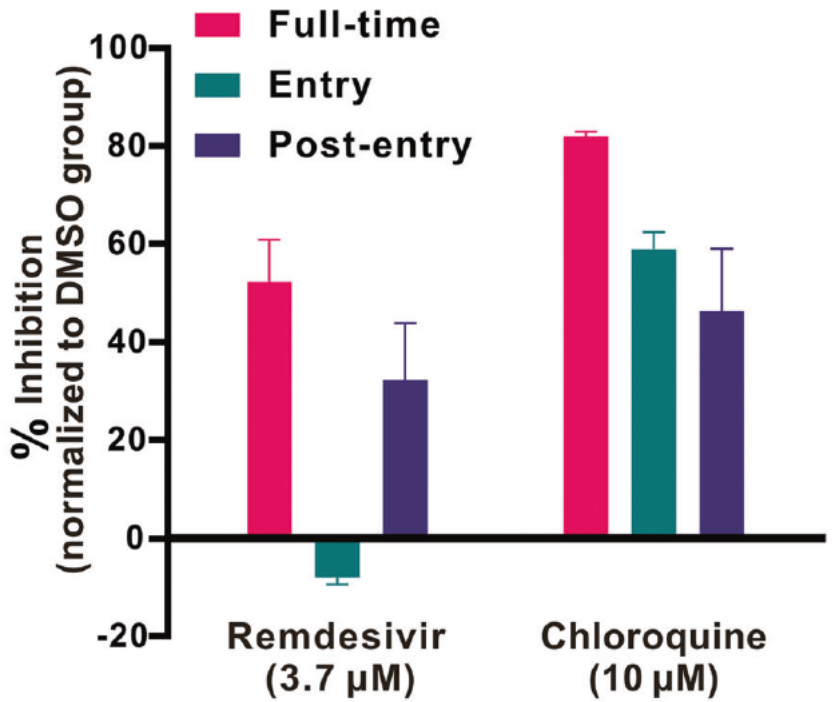
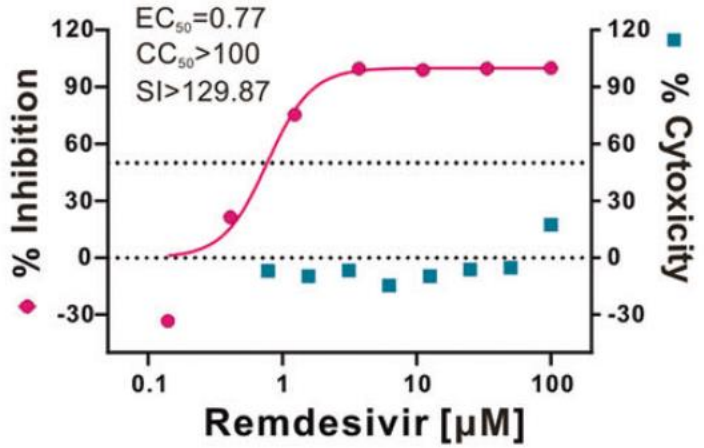


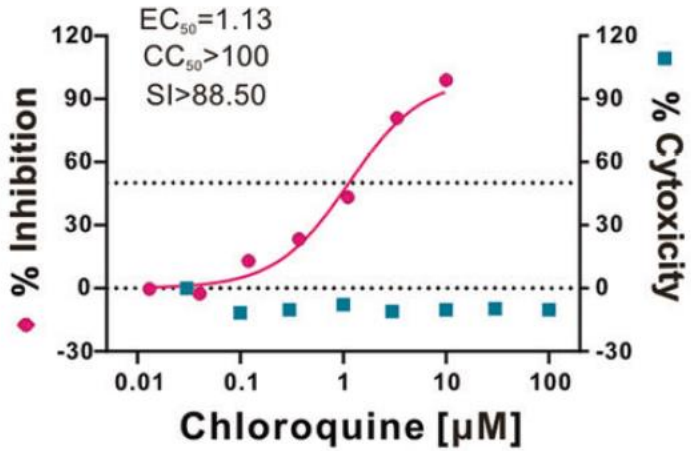
Fig. 1 RDV and IFNb have superior antiviral activity to LPV and RTV. Graphs depict mean % inhibition of MERS-CoV replication (left *Y*-axis) and % cytotoxicity (right *Y*-axis) of antivirals. Calu-3 cells were infected in sextuplicate with MERS-CoV nanoluciferase (nLUC) at a multiplicity of infection (MOI) of 0.08 in the presence of a dose response of drug for 48 h, after which replication was measured through quantitation of MERS-CoV-expressed nLUC. Cytotoxicity was measured in similarly treated but uninfected cultures via Cell-Titer-Glo assay. Representative data are shown from four independent experiments.

Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro

Cell Research (2020) 30:269–271; https://doi.org/10.1038/s41422-020-0282-0







Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro

Ka-Tim Choy[a], Alvina Yin-Lam Wong[a], Prathanporn Kaewpreedee[a], Sin Fun Sia[a], Dongdong Chen[a], Kenrie Pui Yan Hui[a], Daniel Ka Wing Chu[a], Michael Chi Wai Chan[a], Peter Pak-Hang Cheung[b], Xuhui Huang[b], Malik Peiris[a], Hui-Ling Yen[a,*]

[a] *School of Public Health, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China*
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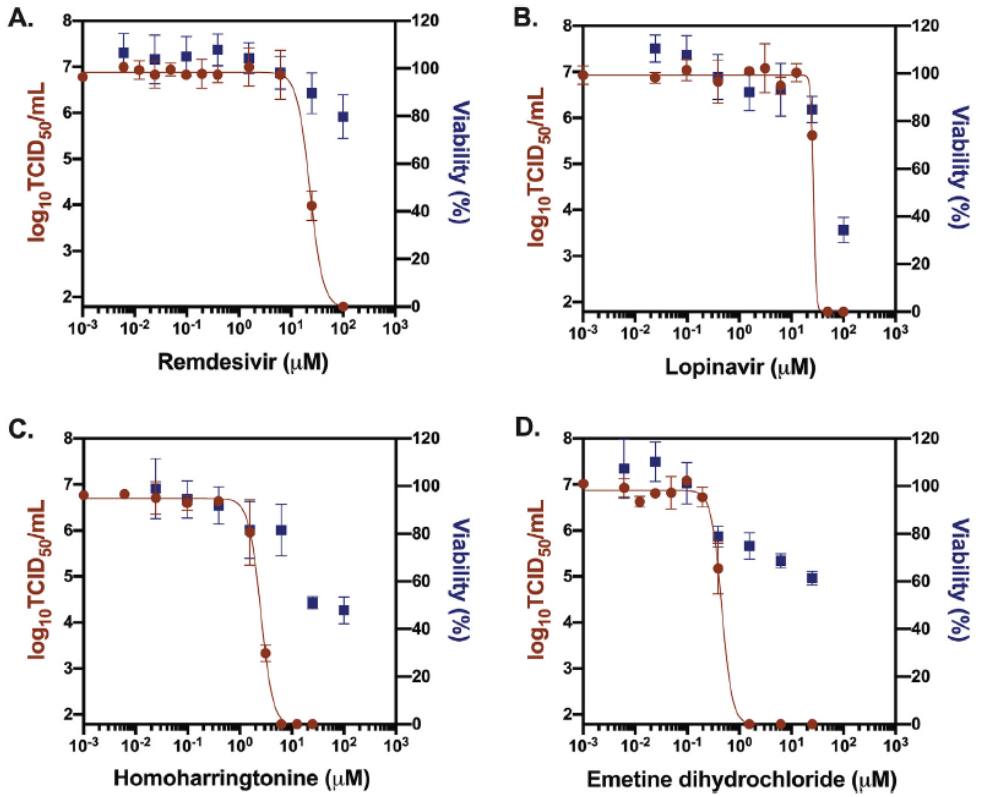

ntiviral activity of remdesivir (A), lopinavir (B), homorringtonine (C) and emetine dihydrochloride (D) against SARS-CoV-2 virus in vitro. ; viral loads ($log_{10}TCID_{50}$/mL left Y axis) and viability (normalized to the ATP level of the Vero E6 cells incubated with infection media) under increasing ıtions of the antiviral compounds are shown.

Choy K.T. , et al. *Antiviral Research 178 (2020) 104786*

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

Yeming Wang, Dingyu Zhang*, Guanhua Du*, Ronghui Du*, Jianping Zhao*, Yang Jin*, Shouzhi Fu*, Ling Gao*, Zhenshun Cheng*, Qiaofa Lu*, Yi Hu*, Guangwei Luo*, Ke Wang, Yang Lu, Huadong Li, Shuzhen Wang, Shunan Ruan, Chengqing Yang, Chunlin Mei, Yi Wang, Dan Ding, Feng Wu, Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, Guohui Fan, Fei Zhou, Zhibo Liu, Xiaoying Gu, Jiuyang Xu, Lianhan Shang, Yi Zhang, Lianjun Cao, Tingting Guo, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jaki, Frederick G Hayden, Peter W Horby, Bin Cao, Chen Wang*

	Remdesivir group (n=158)	Placebo group (n=78)	Difference*
Time to clinical improvement	21·0 (13·0 to 28·0)	23·0 (15·0 to 28·0)	1·23 (0·87 to 1·75)†
Day 28 mortality	22 (14%)	10 (13%)	1·1% (–8·1 to 10·3)
Early (≤10 days of symptom onset)	8/71 (11%)	7/47 (15%)	–3·6% (–16·2 to 8·9)
Late (>10 days of symptom onset)	12/84 (14%)	3/31 (10%)	4·6% (–8·2 to 17·4)
Clinical improvement rates			
Day 7	4 (3%)	2 (3%)	0·0% (–4·3 to 4·2)
Day 14	42 (27%)	18 (23%)	3·5% (–8·1 to 15·1)
Day 28	103 (65%)	45 (58%)	7·5% (–5·7 to 20·7)
Duration of invasive mechanical ventilation, days	7·0 (4·0 to 16·0)	15·5 (6·0 to 21·0)	–4·0 (–14·0 to 2·0)
Duration of invasive mechanical ventilation in survivors, days‡	19·0 (5·0 to 42·0)	42·0 (17·0 to 46·0)	–12·0 (–41·0 to 25·0)
Duration of invasive mechanical ventilation in non-survivors, days‡	7·0 (2·0 to 11·0)	8·0 (5·0 to 16·0)	–2·5 (–11·0 to 3·0)
Duration of oxygen support, days	19·0 (11·0 to 30·0)	21·0 (14·0 to 30·5)	–2·0 (–6·0 to 1·0)
Duration of hospital stay, days	25·0 (16·0 to 38·0)	24·0 (18·0 to 36·0)	0·0 (–4·0 to 4·0)
Time from random group assignment to discharge, days	21·0 (12·0 to 31·0)	21·0 (13·5 to 28·5)	0·0 (–3·0 to 3·0)
Time from random group assignment to death, days	9·5 (6·0 to 18·5)	11·0 (7·0 to 18·0)	–1·0 (–7·0 to 5·0)

Lancet , Published online April 29, 2020 https://doi.org/10.1016/S0140-6736(20)31022-9

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

Yeming Wang, Dingyu Zhang*, Guanhua Du*, Ronghui Du*, Jianping Zhao*, Yang Jin*, Shouzhi Fu*, Ling Gao*, Zhenshun Cheng*, Qiaofa Lu*, Yi Hu*, Guangwei Luo*, Ke Wang, Yang Lu, Huadong Li, Shuzhen Wang, Shunan Ruan, Chengqing Yang, Chunlin Mei, Yi Wang, Dan Ding, Feng Wu, Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, Guohui Fan, Fei Zhou, Zhibo Liu, Xiaoying Gu, Jiuyang Xu, Lianhan Shang, Yi Zhang, Lianjun Cao, Tingting Guo, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jaki, Frederick G Hayden, Peter W Horby, Bin Cao, Chen Wang*

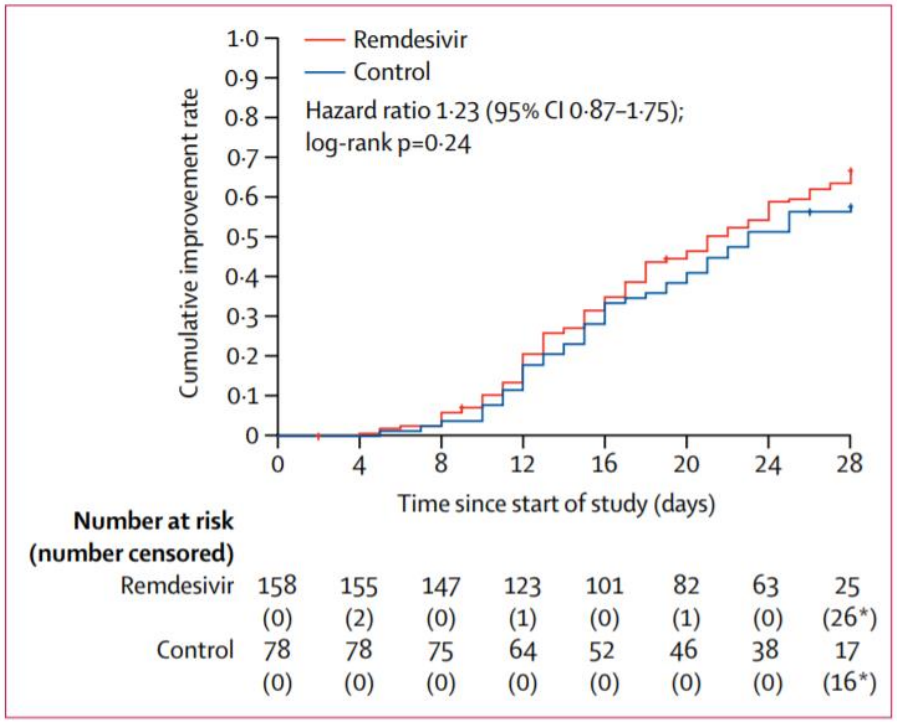

Figure 2: **Time to clinical improvement in the intention-to-treat population**
Adjusted hazard ratio for randomisation stratification was 1·25 (95% CI 0·88–1·78). *Including deaths before day 28 as right censored at day 28, the number of patients without clinical improvement was still included in the number at risk.

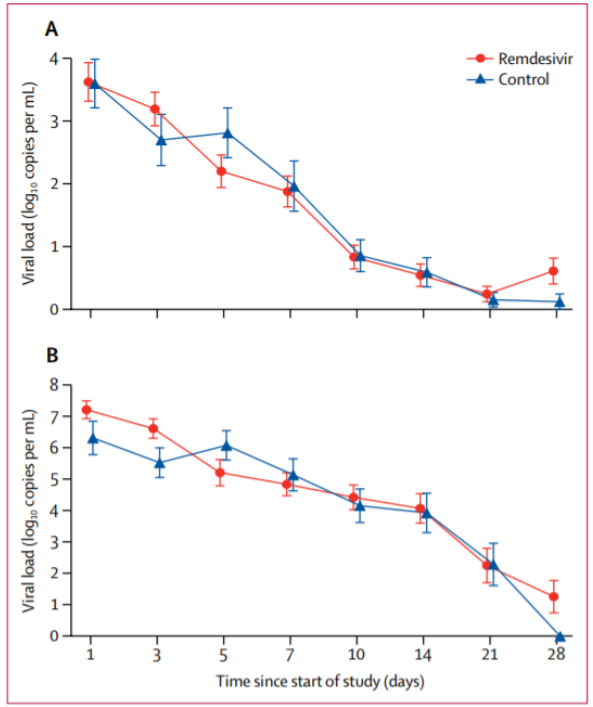

Figure 3: **Viral load by quantitative PCR on the upper respiratory tract specimens (A) and lower respiratory tract specimens (B)**
Data are mean (SE). Results less than the lower limit of quantification of the PCR assay and greater than the limit of qualitative detection are imputed with half of actual value; results of patients with viral-negative RNA are imputed with 0 log_{10} copies per mL.

Lancet , Published online April 29, 2020 https://doi.org/10.1016/S0140-6736(20)31022-9

Mécanismes d'action de la chloroquine et de l'hydroxy chloroquine

Chloroquine et hydroxychloroquine

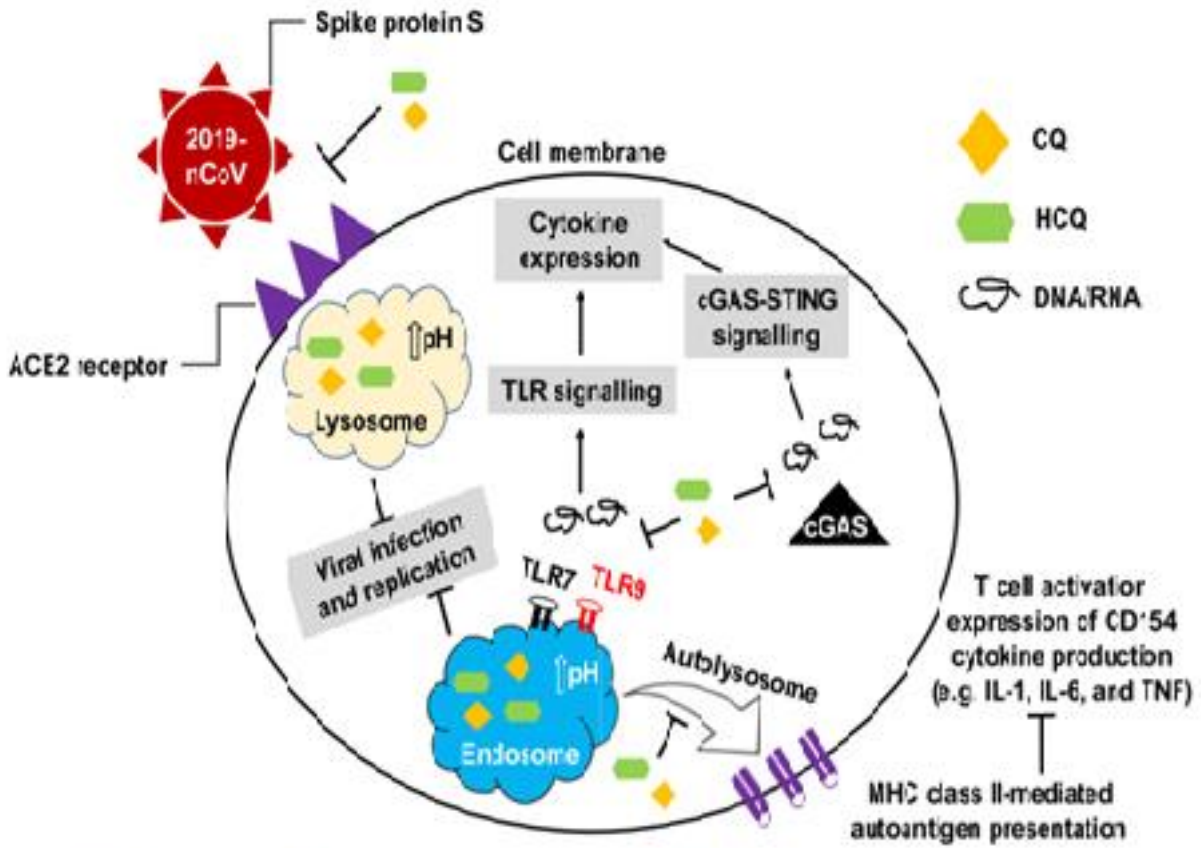

Figure 2. A graphical illustration of the antiviral mechanisms of CQ and HCQ. Both chemicals can interfere with the glycosylation of ACE2 and reduce the binding efficiency between ACE2 on the host cells and the spike protein on the surface of the coronavirus. They can also increase the pH of endosomes and lysosomes, through which the fusion process of the virus with host cells and subsequent replication are prevented. When HCQ enters APCs, it prevents antigen processing and MHC class II-mediated autoantigen presentation to T cells. The subsequent activation of T cells and expression of CD154 and other cytokines are repressed. In addition, HCQ disrupts the interaction of DNA/RNA with TLRs and the nucleic acid sensor cGAS and therefore the transcription of pro-inflammatory genes cannot be stimulated. As a result, administration of CQ or HCQ not only blocks the invasion and replication of coronavirus, but also attenuates the possibility of cytokine storm. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

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Original Investigation | Infectious Diseases

Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection

A Randomized Clinical Trial

Mayla Gabriela Silva Borba, MD; Fernando Fonseca Almeida Val, PhD; Vanderson Souza Sampaio, PhD; Marcia Almeida Araújo Alexandre, MD; Gisely Cardoso Melo, PhD; Marcelo Brito, MSc; Maria Paula Gomes Mourão, MD; José Diego Brito-Sousa, MSc; Djane Baía-da-Silva, PhD; Marcus Vinitius Farias Guerra, MD; Ludhmila Abrahão Hajjar, MD; Rosemary Costa Pinto, BSc; Antonio Alcirley Silva Balieiro, MSc; Antônio Guilherme Fonseca Pacheco, MD; James Dean Oliveira Santos Jr, PhD; Felipe Gomes Naveca, PhD; Mariana Simão Xavier, MSc; André Machado Siqueira, MD; Alexandre Schwarzbold, MD; Júlio Croda, MD; Maurício Lacerda Nogueira, MD; Gustavo Adolfo Sierra Romero, MD; Quique Bassat, MD; Cor Jesus Fontes, MD; Bernardino Cláudio Albuquerque, MD; Cláudio-Tadeu Daniel-Ribeiro, MD; Wuelton Marcelo Monteiro, PhD; Marcus Vinícius Guimarães Lacerda, MD; for the CloroCovid-19 Team

Table 2. Safety Outcomes in the Intention-to-Treat Population Until Day 13[a]

Variable	No/ total No. (%)					
	All patients			COVID-19 confirmed cases		
	Total	Low-dosage group[b]	High-dosage group[c]	Total	Low-dosage group[b]	High-dosage group[c]
Hemoglobin decreased[d]	11/42 (26.2)	4/18 (22.2)	7/24 (19.2)	7/29 (24.1)	3/11 (27.3)	4/18 (22.2)
Creatinine increased[e]	16/38 (42.1)	7/15 (46.7)	9/23 (39.1)	13/27 (48.1)	5/9 (55.6)	8/18 (44.4)
CK increased	13/33 (39.4)	6/19 (31.6)	7/14 (50.0)	9/24 (37.5)	3/15 (20.0)	6/9 (66.7)
CKMB increased	10/26 (38.4)	3/13 (23.1)	7/13 (53.8)	7/22 (31.8)	3/13 (23.1)	4/9 (44.4)
QTcF >500 ms[f]	11/73 (15.1)	4/36 (11.1)	7/37 (18.9)	8/57 (14.0)	1/27 (3.6)	7/29 (24.1)
Ventricular tachycardia	2/73 (2.7)	0/36	2/37 (2.7)	2/62 (3.2)	0/31	2/31 (6.5)

Abbreviation: CK, creatine phosphokinase; CKMB, creatinine phosphokinase-MB; COVID-19, coronavirus disease 2019; QTcF, QT interval corrected by the Fridericia method.

[a] Not all patients completed day 13 visit before this article was finalized.

[b] Low-dosage group received chloroquine for 5 days (450 mg twice daily on the first day and 450 mg once daily for 4 days).

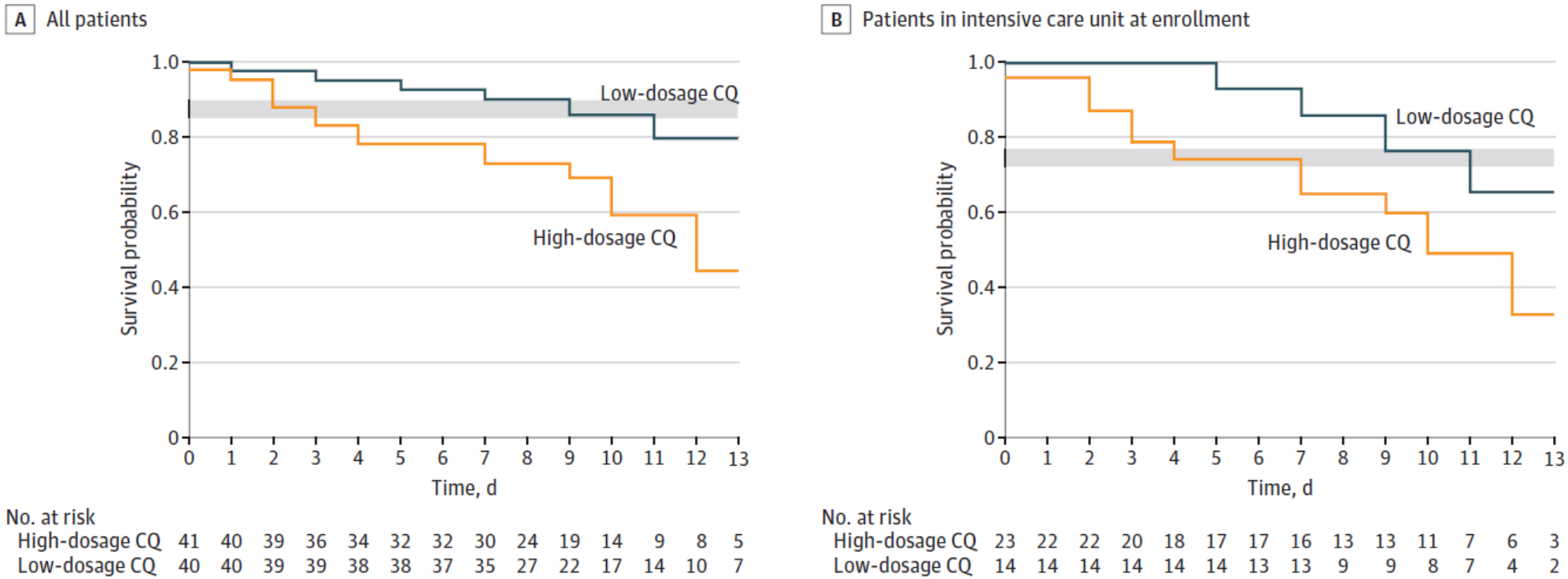
[c] High-dosage group received chloroquine for 10 days (600 mg twice daily for 10 days).

[d] Decreases in hemoglobin level of more than 3 g/dL or 30% or greater from baseline are shown.

[e] Increases in creatinine serum levels of 30% or more from baseline are shown.

[f] Serious adverse events related to the trial regimen were prolongation of the QTcF.

Figure 2. Time From Randomization to Death Among Patients Treated With Each Chloroquine (CQ) Dosage



A, The gray band represents the upper and lower limits of the confidence interval for lethality in hospitalized patients not receiving CQ obtained by Zhou et al[7] and Chen et al[23] (ie, 167 of 990 patients [16.9%]; 95% CI, 14.5%-19.2%). B, The gray band represents the upper and lower limits of the confidence interval for lethality in critically ill patients not receiving CQ in the study by Grasselli et al[24] (ie, 405 of 1581 [25.6%]; 95% CI, 23.5%-27.8%).

Table 3. Clinical Details of 5 Patients Enrolled in the High-Dosage Group With Previous Cardiac Disease

Age, y	Sex	Race	First QTcF, ms	Previous cardiac disease	Other comorbidities	Death
70s	Woman	Black	478	Heart failure	Hypertension, diabetes, and chronic kidney disease	No
60s	Man	Mixed	488	Coronary chronic disease	Hypertension and diabetes	Yes
40s	Woman	White	457	Heart failure	Chronic obstructive pulmonary disease and obesity	No
60s	Man	Mixed	440	Coronary chronic disease	None	Yes
70s	Man	White	NA	Atrioventricular block	Hypertension	Yes

Abbreviations: NA, not available; QTcF, QT interval corrected by the Fridericia method.

Azithromycine

Clinical Pharmacology Perspectives on the Antiviral Activity of Azithromycin and Use in COVID-19

Bharat Damle[1]; Manoli Vourvahis[1]; Erjian Wang[2];

Table 1. In Vitro Antiviral Activity of Azithromycin

Targeted Virus	Antiviral Activity Screening System	Time of Drug Addition to Infected Cell Culture	Incubation Period	MOI	IC_{50} OR EC_{50} (μM)	CC_{50} (μM)	SI[a]	Reference
SARS-CoV-2	Vero cells	15 min pre-treatment	72 h	0.002	2.12 EC_{90}: 8.65	>40	>19	(4)
Zika	Vero cells Huh7 cells A549 cells Hela cells	12 h pre-treatment	48 h	0.1	6.59 1.23-4.97 4.44 -	810 1360 - 3560	123 >273	(8)
	U87 cells Astrocytes	>1 h pre-treatment	48 h	0.01 0.1 3.0 1.0	2.1 2.9 5.1 15	53 44	25 18 10 2.9	(9)
Ebola	Ebola VLP entry assay (Hela cells)	1 h pre-treatment	2 h	N/A	2.79 IC_{90}: 15.8	>500	>179	(10)
	Ebola pseudovirion entry assay (Hela cells)	8 h pre-treatment	72 h	N/A	0.69 IC_{90}: 4.16	-	-	(11)
	Pseudotype Ebola entry assay (Hela cells)	1 h pre-treatment	19 h	N/A	1.3			(12)

Table 3. Selected Clinical Studies in Respiratory Viral Infections

Study Population	Study design	Treatments	Key Results	Conclusion	Reference
COVID-19, >12 yrs (N=36)	Observational, non-randomized, external control, open-label	• Non-randomized Control • HCQ (200 mg q8h x 10 days) • HCQ + AZ (500 mg D1 and 250 mg D2-5)	At D6 post-inclusion, negative nasopharyngeal PCR in: 100% (6/6) pts. HCQ + AZ 57.1% (8/14) HCQ 12.5% controls (p<0.001).	The authors concluded that HCQ is significantly associated with viral load reduction and its effect is reinforced by azithromycin. Additional studies are needed in more severe patient population (NEWS score) with a robust control group.	(2)
COVID-19, >18 yrs (N=80)	Observational, single arm	• HCQ (200 mg q8h x 10 days) + AZ (500 mg D1 and 250 mg D2-5)	Decrease in nasopharyngeal viral load (qPCR): 83% negative at D7, and 93% at D8. Patients presumably contagious (PCR Ct <34) decreased and reached zero on D12.	The authors concluded that these results corroborated the efficacy of HCQ with AZ and its potential effectiveness in the early impairment of contagiousness. This finding provides further evidence in uncontrolled case series, deserving replication.	(3)
COVID-19, 20-77 yrs, (N=11)	Observational, single arm	• HCQ + AZ (unspecified doses)	Within 5 days, one patient died, two were transferred to the ICU. One patient discontinued after 4 days due to QT interval of 460 msec to 470	No evidence of strong antiviral activity with the combination of HCQ and AZ.	(27)

Lopinavir

European Review for Medical and Pharmacological Sciences 2020; 24: 3390-3396

Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019

X.-T. YE[1], Y.-L. LUO[1], S.-C. XIA[2], Q.-F. SUN[1], J.-G. DING[1], Y. ZHOU[1], W. CHEN[1], X.-F. WANG[1], W.-W. ZHANG[1], W.-J. DU[2], Z.-W. RUAN[3], L. HONG[1]

[1]Department of Infection, Rui'an People's Hospital, Rui'an, China
[2]Leading Group for COVID-19, Rui'an People's Hospital, Rui'an, China
[3]Emergency Intensive-Care Unit, Rui'an People's Hospital, Rui'an, China

Table I. General clinical data of the patients.

Features	Test group (n=42)	Control group (n=5)	*p*-value
Gender			0.3525
Male	21	1	
Female	21	4	
Hypertension			0.9977
Yes	7	1	
No	35	4	
Diabetes mellitus			0.9986
Yes	7	1	
No	35	4	
CT abnormality			1.0000
Yes	27	4	
No	12	1	
Body temperature at admission (°C)	37.36±0.67	37.92±0.61	0.7762
Oxygen saturation	97.4±1.52	95.72±9.06	0.6840
Hemoglobin (g/dL)	129.5±10.24	141.06±16.73	0.1399
C-reactive protein (CRP)			0.2670
<10 mg/L	27	2	
>10 mg/L	8	2	

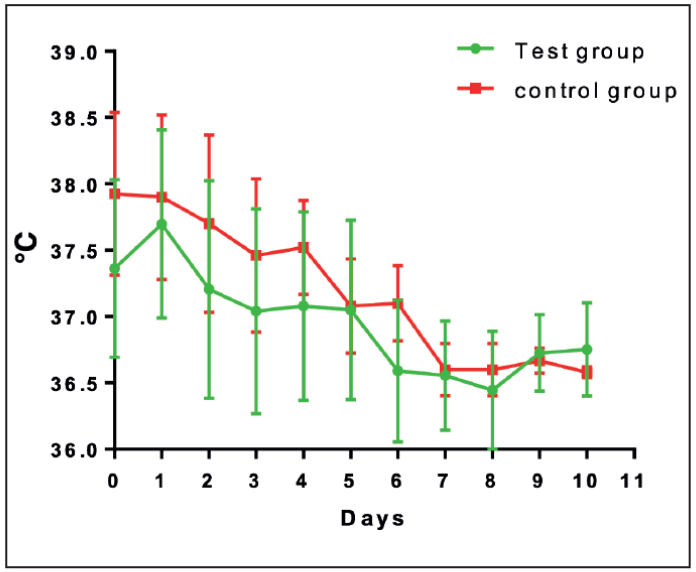


Figure 1. Daily temperature variations of patients in the two groups during 10-day hospitalization period.

The NEW ENGLAND JOURNAL of MEDICINE

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

B. Cao, Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, L. Ruan, B. Song, Y. Cai,

- Premier essai chez l'homme
- 99 patients traités et 100 patients contrôles ayant une pneumonie sévère. Age médian 50 ans.
- traités en médiane 13 jours après début des symptômes
- 30% dans les 2 groupes ont reçu des corticoïdes
- **Pas de différence en terme d'amélioration clinique et de mortalité et de décroissance virologique.**
- Effets secondaires : surtout digestifs

DOI: 10.1056/NEJMoa2001282

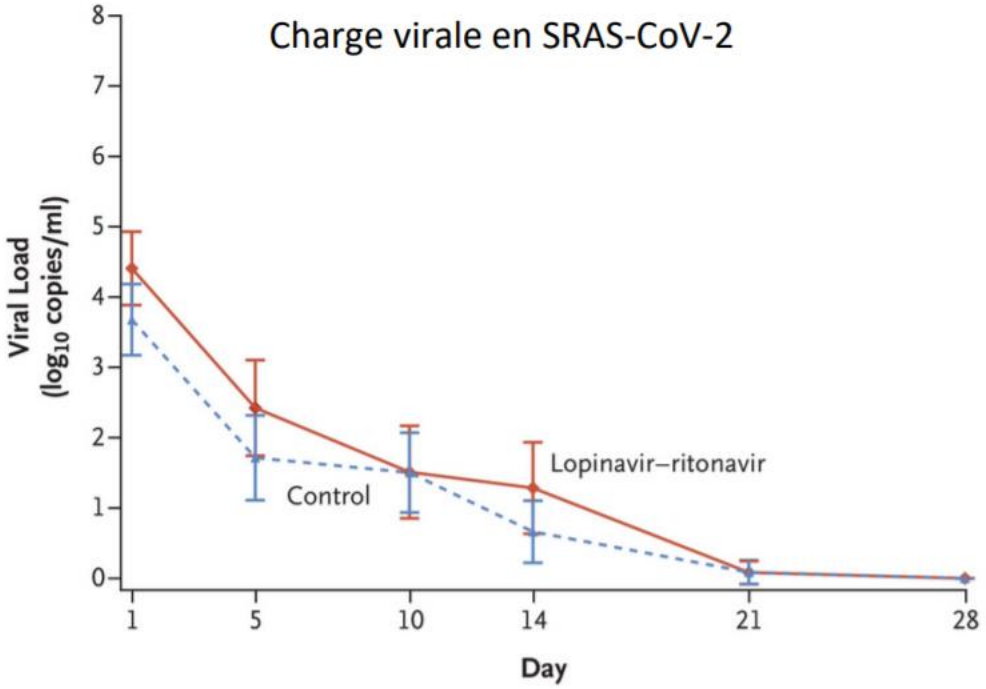
The NEW ENGLAND JOURNAL of MEDICINE

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

B. Cao, Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, L. Ruan, B. Song, Y. Cai,

Pas de différence de la charge virale dans les prélèvements de gorge au cours du temps entre les deux groupes

Les événements indésirables gastro-intestinaux étaient plus fréquents dans le groupe lopinavir – ritonavir, mais les événements indésirables graves étaient plus fréquents dans le groupe soins standard



DOI: 10.1056/NEJMoa2001282

First author; Year; Country	Sample Size	Age (year)*	Male	Status of patients	Antiviral agent	Antiviral treated patients (n)	Dosage	Route of administration	Duration of treatment	Combination	Main findings
Randomized clinical trial											
Cao et al; 2020; China (10)	199	58 (50 to 68)	120	Severe COVID-19 patients	Lopinavir/ Ritonavir	99	400 mg/100 mg twice daily	Oral	14	Yes	Lopinavir–ritonavir administration is not superior to standard care in management of adult patients with severe COVID-19. Clinical improvement and mortality rate are similar in lopinavir–ritonavir treated and standard care groups.
Case-series											
Chen N; 2020; China (11)	99	21 to 82	67	COVID-19 patients	Oseltamivir	75	75 mg twice a day	Oral	3 to 14	Yes	Recovery rate: 31%; Mortality rate: 11%
Chen Q; 2020; China (12)	9	14 to 56	5	Symptomatic COVID-19	Lopinavir/ Ritonavir	9	800 mg/200 mg daily	Oral	4 to 11	Yes	No mortality. Time from onset of treatment to negative result of Cov-test was 4-11 days. Length of hospital stay was 9 to 20 days.
Guan W; 2020; China (13)	1099	47.0 (IQR: 35.0–58.0)	637	Non-severe and severe COVID-19 patients	Oseltamivir	393	NR	NR	NR	Yes	Administration of oseltamivir did not decrease ICU admission and need for ventilator or death
Hu Z; 2020; China (15)	24	5 to 95	8	Asymptomatic COVID-19 infection	Not specified	21	NR	NR	NR	Yes	No mortality, no ICU admission, no severe complication
Huang C; 2020; China (16)	41	49 (IQR 41.0–58.0)	30	Symptomatic COVID-19	Oseltamivir	38	NR	NR	NR	Yes	6 patients died 28 patients were discharged
Liu K; 2020; China (19)	137	20 to 83	61	Severe COVID-19	Not specified	105	NR	NR	NR	Yes	16 patients died during the study.
Liu L; 2020; China (20)	51	16 to 68	32	Discharged COVID-19 patients	Lopinavir/ Ritonavir Oseltamivir Arbidol	51, 7, 2	NR	Oral	NR	Yes	Duration of hospital stay was 9-13 days. 1 patient died.
Qin X; 2020; China (21)	89	23 to 86	45	All COVID-19 patients admitted to a center	Lopinavir/ Ritonavir, Other anti-viral	84, 5	NR	NR	NR	Yes	16 patients were discharged and 1 patient died.

Shang J; 2020; China (22)	416	49 (IQR: 36-61)	194	Survived and dead COVID-19 patients	Not specified	380	NR	NR	NR	Yes	Anti-viral administration did not affect mortality rate (5.6% in non-treated vs. 12.9 treated; p=0.288)
Wang D; 2020; China (23)	138	22 to 92	75	ICU and Non-ICU admitted COVID-19 patients	Oseltamivir	124	NR	NR	NR	Yes	6 patients died and 36 patients were admitted to ICU.
Wu J; 2020; China (25)	80	46.10 Âś 15.42	39	All severity ranges of COVID-19	Ribavirin	80	NR	NR	2-12 days	Yes	21 patients were discharged and 59 patients remained in hospital.
Xu X; 2020; China (26)	62	41 (IQR: 32-52)	35	Symptomatic COVID-19	Lopinavir/ ritonavir, Arbidol, Lopinavir/ ritonavir + Arbidol	25, 1, 21	Lopinavir 400 mg twice daily ritonavir 100 mg twice daily, Arbidol 200 mg three time daily	NR	NR	Yes	One patient was discharged. Other patients remained in hospital
Yang W; 2020; China (27)	149	45.11 Âś 13.35	81	All COVID-19 patients admitted to a center	Not specified	140	NR	NR	NR	Yes	No mortality. 73 patients were discharged and 76 remained in hospital.
Young BE; 2020; Singapore (28)	18	31 to 73	9	Symptomatic COVID-19	Lopinavir/ ritonavir	5	NR	NR	NR	Yes	Two patients recovered and the condition of 2 other patients deteriorated. Only one patient completed the 12-day planned protocol. Four patients experienced side effects of antiviral therapy
Zhang G; 2020; China (29)	221	20 to 96	108	Non-severe and severe confirmed COVID-19 patients	Not specified	196	NR	NR	NR	Yes	12 patients died. Chest CT improved after administration of ECMO and IMV
Zhou Z; 2020; China (31)	10	29 to 68	8	Confirmed COVID-19 patients	Lopinavir/ ritonavir, Arbidol	8, 3	NR	Oral	NR	Yes	1 patient died, 5 patients remained hospitalized and 4 patients were discharged

Case reports										
Han X; 2020; China (14)	1	23	1	Diabetic patient with COVID-19	Oseltamivir/ Gan-civlovire	1	NR	NR	15	Yes	Patient was discharged from hospital after 15 days
Li W; 2020; China (17)	5	10 months to 6 years	4	Children with COVID-19	Not specified	2	NR	NR	NR	Yes	The antiviral therapy did not change the outcome or length of stay
Lim J; 2020; South Korea (18)	1	54	1	Symptomatic COVID-19 patient	Lopinavir/ ritonavir	1	75 mg twice a day/50 mg twice daily	Oral	9	Yes	Good recovery. It is not clear that the decreased load of virus is due to the nature of healing process or a result of anti-viral therapy
Wang Z; 2020; China (24)	4	19 to 63	3	COVID-19 patients	Lopinavir/ ritonavir, Arbidol, SFJDC	4	400 mg/100 mg twice daily, 0.2 g, three time daily, 2.08 g, three time daily	Oral	6-16 days	Antibiotic	2 patients recovered and 2 patients remained in hospital
Zhang Z; 2020; China (30)	2	38	1	Symptomatic COVID-19 patients	oseltamivir and Arbidol	2	NR	NR	NR	Yes	Both patients recovered and were discharged

* Age was reported as range, meanÂśSD or median (interquartile rang [IQR]). ECMO: extracorporeal membrane oxygenation; IMV: invasive mechanical ventilation; NR: Not reported; ICU: intensive care unit; CT: computed tomography

DISCOVERY Trial

Projet européen qui va évaluer 4 stratégies thérapeutiques (attribuées aléatoirement) :

- soins standards
- soins standards + remdesivir,
- soins standards + lopinavir /ritonavir,
- soins standards + lopinavir, ritonavir + interféron bêta
- soins standards + hydroxy-chloroquine.

Essai Randomisé Contrôlé

Mais pas en double aveugle

3200 patients européens incluant la Belgique, les Pays-Bas, le Luxembourg, le Royaume uni, l'Allemagne et l'Espagne

SOLIDARITY Trial

Projet international qui va évaluer 4 stratégies thérapeutiques (attribuées aléatoirement) :

- soins standards
- soins standards + remdesivir,
- soins standards + lopinavir /ritonavir,
- soins standards + lopinavir, ritonavir + interféron bêta
- soins standards + hydroxy-chloroquine.

Essai Randomisé Contrôlé

Mais pas en double aveugle

Inclut l'Argentine, le Bahreïn, la France, le Canada, L'Iran, la Norvège, l'Afrique du Sud, l'Espagne, la Suisse et la Thaïlande

Arbidol

Arbidol

- **Umifénovir**, commercialisé en Russie et en Chine pour la grippe
- C'est un inhibiteur de fusion
- Essais cliniques associés à d'autres antiviraux

Current Medicinal Chemistry, 2008, *15*, 997-1005

Arbidol: A Broad-Spectrum Antiviral Compound that Blocks Viral Fusion

Y.S. Boriskin[1], I. A. Leneva[2], E.-I. Pécheur[3] and S. J. Polyak*[,4]

[1]Institute of Virology, Moscow, Russia; [2]Chemical and Pharmaceutical Institute, Moscow, Russia; [3]IBCP; CNRS, UMR 5086; Université Lyon 1; IFR 128, Lyon, France; [4]Department of Laboratory Medicine, University of Washington, School of Medicine, Seattle, USA

Table 1
Viruses against which ARB has demonstrated antiviral activity. Virion type: E, enveloped; NE, non-enveloped. References in bold report animal studies of ARB antiviral activity. See text for details and abbreviations.

Family	Virus	Virion type	*In vitro* IC50 (μM)	*In vivo* (mg/kg/day)	DAA/HTA	References
Orthomyxoviridae	Influenza	E	2.5–16 A/H3N2 12 B 13.3	A/H3N2 2–50 A/H1N1 100 A/H1N1 90–180 A 15–30	Both	**Brooks et al. (2012)**, Fediakina et al. (2005, 2011), Leneva and Shuster (2006), **Leneva et al. (2010), Liu et al. (2013b), Loginova et al. (2008), Shi et al. (2007)**
Paramyxoviridae	RSV	E	16	–	nd/HTA	Shi et al. (2007)
			no IC50	10–50	nd/HTA	**Brooks et al. (2012)**
Picornaviridae	Poliovirus 1	NE	0.41	–	nd/HTA	Brooks et al. (2012)
	Rhinovirus 14	NE	12.2	–	nd/HTA	idem
	Coxsackie B5	NE	5	50	Both	**Zhong et al. (2009)**
Bunyaviridae	Hantaan	E	2	5–20	Both	**Deng et al. (2009), Wei et al. (2013)**
Rhabdoviridae	VSV	E	14	–	nd/HTA	Blaising et al. (2013)
Reoviridae	Reovirus T1L	NE	10	–	nd/HTA	Blaising et al. (2013)
Togaviridae	Chikungunya	E	12.2	–	not DAA/HTA	Delogu et al. (2011)
Hepadnaviridae	HBV	E	DNA replic 43 HBsAg 90	–	nd/HTA	Zhao et al. (2006)
Flaviviridae	HCV	E	2–11.3	–	Both	Blaising et al. (2013), Boriskin et al. (2006, 2008), Haid et al. (2009), Pécheur et al. (2007), Teissier et al. (2011)

Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19

Zhen Zhu[a,b,1], Zhaohui Lu[c,1], Tianmin Xu[d], Cong Chen[e], Gang Yang[c], Tao Zha[f], Jianchun Lu[a,g], Yuan Xue[a,g,*]

Laboratory and radiology findings of patients with COVID-19.

Variables	Lopinavir/ritonavir (n=34)	Arbidol (n=16)
Age, years	40.5(34.8–52.3)	26.5(23.3–52.5)
Male, n (%)	20(58.8)	6(37.5)
Duration of fever, days	2.5(0–5.0)	1.0(0–5.8)
Laboratory findings		
ALT, U/L	20.9(12.2–24.1)	15.7(11.0–30.5)
C-reactive protein, mg/L	7.7(1.9–26.5)	1.1(0.5–16.0)
WBC, E+09/L	5.2(3.9–6.4)	4.5(3.2–6.1)
Neutrophils, E+09/L	3.2(2.4–4.5)	2.1(1.4–3.3)
Lymphocytes, E+09/L	1.1(0.9–1.5)	1.6(1.1–2.0)
D-dimer,μg/mL	0.4(0.3–0.7)	0.3(0.3–0.4)
CT findings		
Unilateral pneumonia, n(%)	6(17.6)	3(18.8)
Bilateral pneumonia, n(%)	27(79.4)	11(68.8)
Ct(*ORF1ab*) <40 on day 7, n(%)	26(76.5)	8(50.0)
Ct(*ORF1ab*) <40 on day 14, n(%)	15(44.1)	0(0)
Duration of positive RNA test, days	11.5(8.8–17.0)	9.5(5.3–11.0)

Data are expressed as median (IQR) and n(%). Comparison was conducted by Kruskal-Wallis test for continuous variables, and Fisher's exact test for categorical values. ALT, alanine aminotransferase; WBC, white blood cells; CT, computer tomography; Ct, cycle threshold.

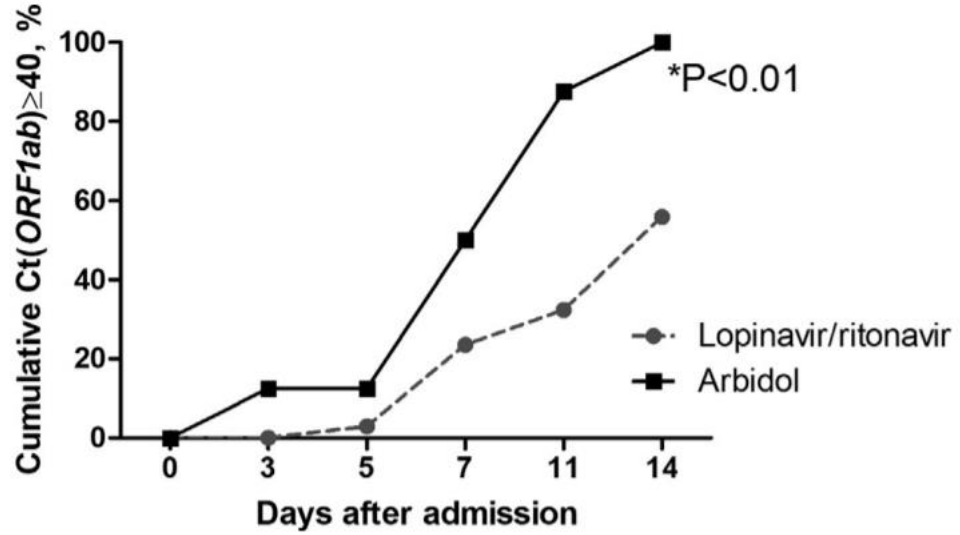


Fig. 1. Dynamic changes of cycle threshold (Ct) values during treatment with lopinavir/ritonavir and arbidol. Ct, cycle threshold.

Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019 : A retrospective study

Ningfang Lian [1†], Hansheng Xie [1†], Su Lin [2], Jiefeng Huang[1], Jianming Zhao [1], Qichang Lin [1*]

Table 2 Effectiveness of umifenovir in patients with COVID-19

	Umifenovir Group (n=45)	Control Group (n=36)	P Value
CT Score (after-treatment)	7 (5- 9)	5 (2- 6)	0.01
CT Score dif	3 (1- 7)	3 (1- 4)	0.52
Time from admission to first negative test of SARS-CoV-2 (days)	6 (4- 8)	3 (1- 7)	0.01
Time from onset of symptoms to first negative test of SARS-CoV-2 (days)	18 (12- 21)	16 (11- 21)	0.42
Negative rate of pharyngeal swab's test for SARS-CoV-2 within 1 week	33 (73.3%)	28 (77.8%)	0.19
Length of hospital stay (days)	13 (9- 17)	11 (9- 14)	0.04

Data were presented as n (%) or median (IQR). Abbreviations: COVID-19, Coronavirus disease

Clinical Microbiology and Infection, doi.org/10.1016/j.cmi.2020.04.026

Tocilizumab

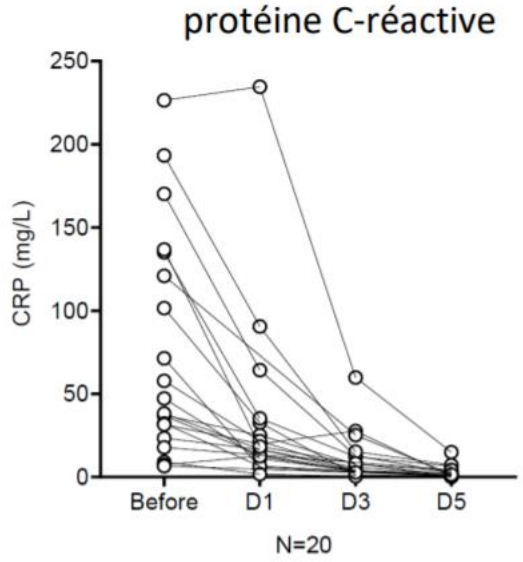
Essai clinique en Chine (Xu) : 21 patients avec symptômes sévères d'âge moyen 56,8 ans (18 hommes et 3 femmes)

Traitement : lopinavir, methylprednisolone + **tocilizumab**

À J+5, la fièvre a diminué

- 75% (15 cas) ont diminué leur apport en oxygène
- Le nombre de lymphocytes, qui a diminué chez 85,0% des patients avant (17/20), est revenu à la normale chez 52,6% des patients (10/19)
- La protéine C-réactive anormalement élevée a diminué de manière significative chez 84,2% des patients (16/19)
- Pas d'effets indésirables

→ Au final, 19 patients (90,5%) ont quitté l'hôpital



Effective Treatment of Severe COVID-19 Patients with Tocilizumab

Xiaoling Xu[1,#*], Mingfeng Han[2,#], Tiantian Li[1], Wei Sun[2], Dongsheng Wang[1], Binqing Fu[3,4], Yonggang Zhou[3,4], Xiaohu Zheng[3,4], Yun Yang[5], Xiuyong Li[6], Xiaohua Zhang[2], Aijun Pan[5], Haiming Wei[3,4*]

Limites :

Essai de très petite taille, pas de randomisation, pas de double aveugle, PAS DE TRAITEMENT CONTRÔLE, pas de tests statistiques précisés, pas de mesure de la charge virale à différents jours

Métronidazole

?

Archives of Academic Emergency Medicine. 2020; 8(1): e40

COMMENTARY

Metronidazole; a Potential Novel Addition to the COVID-19 Treatment Regimen

Reza Gharebaghi[1,2], Fatemeh Heidary[2,3*], Mohammad Moradi[2,4], Maryam Parvizi[2,5]

1. Kish International Campus, University of Tehran, Tehran, Iran.

Table 1: Effects of metronidazole on immunopathological manifestations of COVID-19 infection

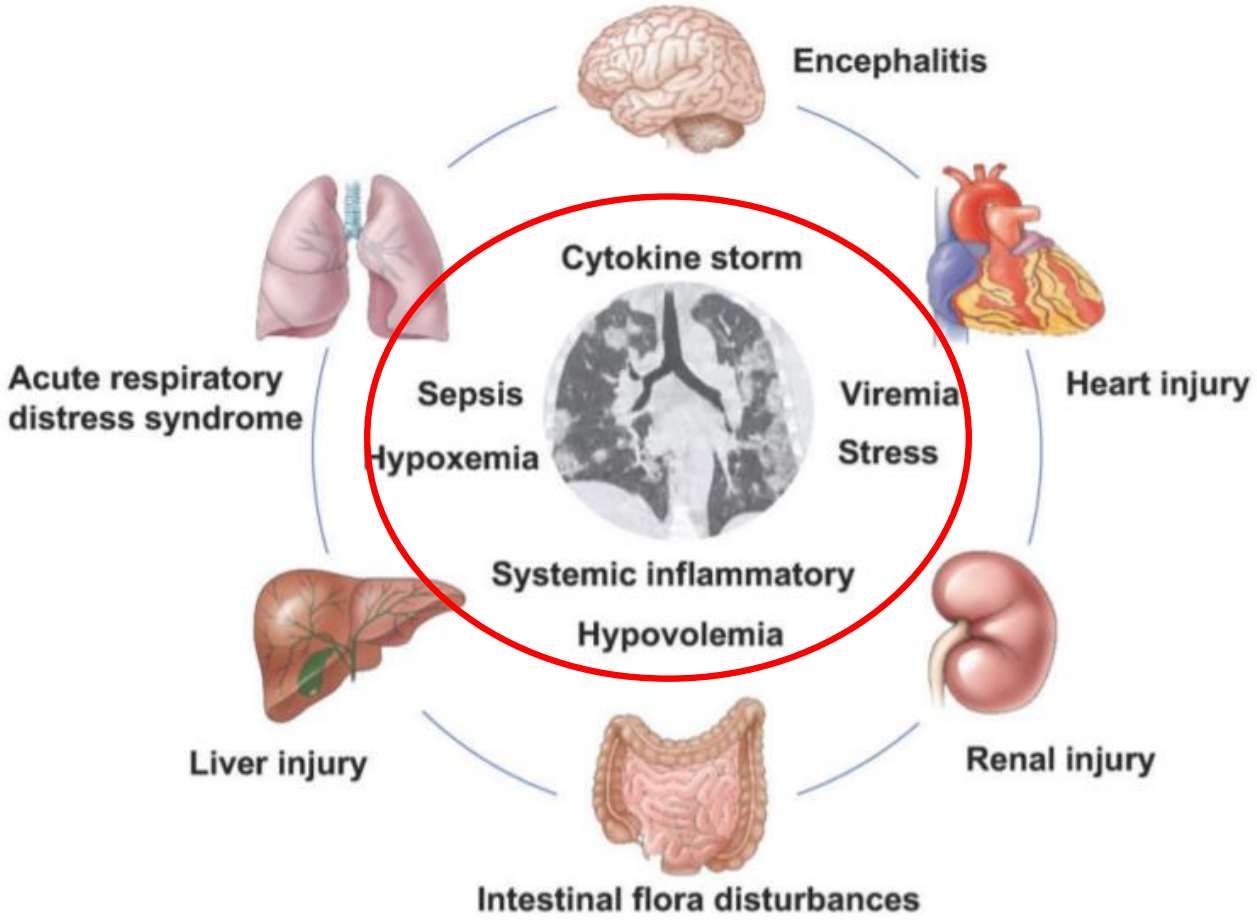
COVID-19	Metronidazole
↑ IL8 (5)	↓ IL8 (10-13)
↑ IL6 (6, 8)	↓ IL6 (10-15)
↑ IL1B (5)	↓ IL1B (10-15)
↑ TNFα (5)	↓ TNFα (11-13, 15-17)
↑ CRP (6)	↓ CRP (11, 12)
↑ IL12 (21)	↓ IL12 (11, 13, 14)
↑ IFNγ (5)	↓ IFNγ (11, 14, 16)
↑ Neutrophils (5, 6)	↓ Neutrophils (11, 17, 18)
↓ Lymphocytes (5, 6, 8)	↑ Lymphocytes (11, 17), lymphoproliferative properties (11, 19)

CRP: C-reactive protein; IFN: interferon; IL: interleukin; TNF: tumor necrosis factor.

Antithrombotiques

- Augmentation de la perméabilité alvéolocapillaire et un œdème interstitiel (opacité en verre dépoli)
- Atteinte de l'endothélium : SARS-Cov-2 : tropisme vasculaire
- Endothélites au niveau du poumon, rein, cœur et intestin grêle
- Un endothélium dysfonctionnel et inflammatoire peut exprimer un facteur tissulaire qui déclenche la coagulation
- **Embolies et microthromboses multi-viscérales**
  - Pulmonaires , cérébrales , digestives (intestin et foie)
  - Rénales et dermatologiques

Corticoïdes



Journal of Clinical and Translational Hepatology 2020 vol. 8 | 13–17

Les autres médicaments

Potential interventions for novel coronavirus in China: A systematic review

TABLE 1 General supportive treatments

Options	Virus targeted and functions related
2.1. Nutritional interventions	
2.1.1. Vitamin A	Measles virus, human immunodeficiency virus, avian coronavirus
2.1.2. B vitamins	MERS-CoV; ventilator-induced lung injury
2.1.3. Vitamin C	Avian coronavirus; lower respiratory tract infections
2.1.4. Vitamin D	Bovine coronavirus
2.1.5. Vitamin E	Coxsackievirus, bovine coronavirus
2.1.6. Omega-3 polyunsaturated fatty acids (PUFA)	Influenza virus, human immunodeficiency virus
2.1.7. Selenium	Influenza virus, avian coronavirus; viral mutations
2.1.8. Zinc	Measles virus, SARS-CoV
2.1.9. Iron	Viral mutations
2.2. Immunoenhancers	
2.2.1. Interferons	SARS-CoV, MERS-CoV
2.2.2. Intravenous gammaglobulin	SARS-CoV
2.2.3. Thymosin α-1	Increase resistance to glucocorticoid-induced death of thymocyte
2.2.4. Thymopentin	Restore antibody production
2.2.5. Levamisole	Immunostimulant agent or immunosuppressive agent
2.2.6. Cyclosporine A	SARS-CoV, avian infectious bronchitis virus
2.2.7. Chinese medicine	SARS-CoV, avian infectious bronchitis virus

Abbreviations: MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus.

J Med Virol. 2020;92:479–490., DOI: 10.1002/jmv.25707

Table 5. Selected Patents Associated with Potential Drugs (Repurposing) for COVID-19 or Small Molecules for Treatment of SARS or MERS

patent no.	priority date	title	organization
WO2009114512	20080311	Preparation of azetidine and cyclobutane derivatives as JAK inhibitors	Incyte Corporation, USA
WO2014028756	20140220	Deuterated baricitinib	Concert Pharmaceuticals, Inc., USA
JP5971830	20150428	Preparation of polycyclic pyridone derivatives as cap-dependent endonuclease (CEN) inhibitors and prodrugs thereof	Shionogi and Co., Ltd., Japan
US20160122374	20141029	Preparation of nucleosides and methods for treating Filoviridae virus infections	Gilead Sciences, Inc., USA
US20170071964	20160916	Preparation of amino acid-containing nucleotides and methods for treating arenaviridae and coronaviridae virus infections	Gilead Sciences, Inc., USA
WO2007075145	20070704	Preparation of benzopyranone derivatives as anti-coronaviral agents	Singapore Polytechnic, Singapore; Shanghai Institute of Materia Medica Chinese Academy of Sciences, China
WO2005021518	20050310	Preparation of 3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acid derivatives as cysLT2 receptor antagonists for treatment of respiratory diseases	Ono Pharmaceutical Co., Ltd., Japan
WO2007120160	20071025	Preparation of N-heterocyclic acetamides useful for viral inhibition	Novartis AG, USA
WO2009119167	20091001	Aniline derivative having anti-RNA viral activity	KinoPharma, Inc., Japan
WO2013049382	20130404	Broad-spectrum antivirals against 3c or 3c-like proteases of picornavirus-like supercluster: picornaviruses, caliciviruses and coronaviruses	Kansas State University Research Foundation; The Ohio State University; Wichita State University - all in USA
WO2018042343	20180308	Preparation of peptides that inhibit 3C and 3CL proteases and methods of use thereof	GlaxoSmithKline, UK
WO2007067515	20070614	Five-membered iminocyclitol derivatives as selective and potent glycosidase inhibitors: new structures for antivirals and osteoarthritis therapeutics	Academia Sinica, Taiwan

https://dx.doi.org/10.1021/acscentsci.0c00272
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Table 8. Target Analysis of Patents on Developing Therapeutic Antibodies for SARS

patent number	antigen of SARS antibody	patent title	organization	priority date
EP2112164	lipid attachment signals or GPI	Antiviral peptides linked to a lipid attachment signals or GPI against enveloped virus such as HIV, avian flu, SARS or Ebola virus	Institute Pasteur of Shanghai	20080229
WO2009128963	spike protein	Cross-neutralizing human monoclonal antibodies to SARS-CoV and methods of use thereof	Institute for Research In Biomedicine	20080117
WO2009128963	spike protein	Cross-neutralizing human monoclonal antibodies to spike protein of SARS coronavirus and methods of use thereof	Humab, LLC	20080117
WO2008035894	viral infection	Preparation of antiviral antibody 3D8 fragments and their use in treatment of viral infection	Sung Kyun Kwan University; Ajou University; Invitroplant Co., Ltd.	20060919
WO2008060331	spike protein	Antibodies to SARS coronavirus	Amgen Inc.	20060519
WO2007044695	spike protein	Neutralizing monoclonal anti-spike protein antibodies for diagnosis and treatment of SARS-coronavirus-associated disease and screening of vaccine or anti-SARS agent	Dana-Farber Cancer Institute	20051007
CN1911963	RBD of S protein	Method for preparing neutralizing monoclonal antibody against severe acute respiratory syndrome coronavirus and its application	Chinese Academy of Sciences	20050810
CN1903878	spike protein	Fab fragment of human antibody IgG against SARS coronavirus	Fudan University	20050726
WO2006095180	S2 protein	Human monoclonal antibodies against SARS-associated coronavirus and treatment of patients with SARS	Ultra Biotech Ltd.; University of California	20050310
WO2006086561	spike protein	Neutralizing monoclonal antibodies against severe acute respiratory syndrome-associated coronavirus	New York Blood Center, Inc.	20050208
CN1664100	spike protein	Preparation of heavy chain and light chain variable regions of anti-SARS coronavirus antigen antibodies and their diagnostic and therapeutic uses thereof	Chen Zhinan	20050204
CN1660912	IL-8	Sequences of monoclonal antibodies against human interleukin 8 and therapeutic use	Ye Qingwei	20041208
WO2006051091	spike protein	Compositions against SARS-coronavirus and uses thereof	Crucell Holland BV	20041111
WO2006051091	spike protein	Compositions against SARS-coronavirus comprising at least two immunoglobulins reacting with non-competing epitopes, and therapeutic and diagnostic uses thereof	Crucell Holland BV	20041111
CN1673231	spike protein	Monoclonal antibody of SARS coronavirus N protein and its use in treatment of SARS virus infections	Chinese Academy of Sciences	20040715
US20060240551	spike protein	Neutralizing monoclonal antibodies against severe acute respiratory syndrome-associated coronavirus	New York Blood Center, Inc.	20040602
WO2005054469	spike protein	Anti-SARS-coronavirus monoclonal antibodies, and diagnostic, therapeutic and vaccine preparation uses	Health Canada	20031205
WO2005060520	spike protein	Antibodies specific to SARS-CoV spike protein for diagnosis and therapy of SARS and for screening of epitopic vaccines or anti-SARS therapeutics	Dana-Farber Cancer Institute, Inc.	20031125
US20050106563	spike protein	Epitope profiles of SARS coronavirus for use in antigen detection, antibody production, and defense against infection	Genesis Biotech Inc.	20030908
US20050069869	spike protein	SARS coronavirus codon-optimized sequences for spike (S) protein expression, anti-S human monoclonal antibodies, and therapeutic and diagnostic uses thereof	University of Massachusetts	20030804
WO2005012360	S and N proteins	Antibody binding molecules specific for SARS coronavirus	Crucell Holland BV	20030722
CN1566155	S, N, and M proteins	Antibody library-derived human monoclonal anti-SARS virus antibodies for treating severe acute respiratory syndrome	Igcon Therapeutics Co., Ltd.; Genetastix Corporation	20030710
WO2005007671	spike protein	Compositions and methods for treating SARS using peptides derived from SARS virus E2 N-terminal-alpha helix or C-terminal-alpha helix and related monoclonal antibody	Epitomics, Inc.	20030429

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Perspectives vaccinales

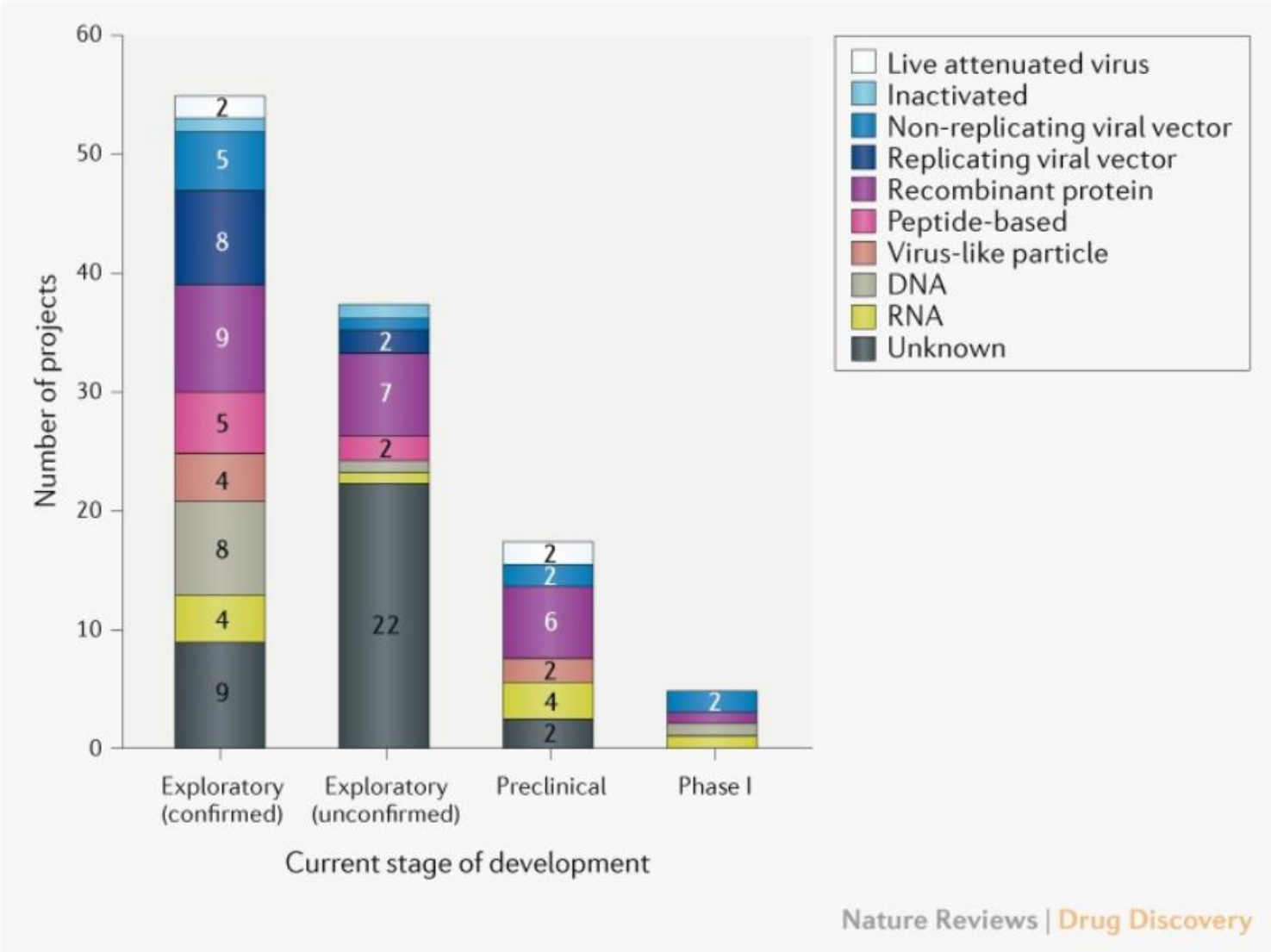


Fig. 1 | **Pipeline of COVID-19 vaccine candidates by technology platform**. Exploratory projects (split into confirmed and unconfirmed) are in the early planning stage with no in-vivo testing, and preclinical projects are at the stage of in-vivo testing and/or manufacturing clinical trials material.

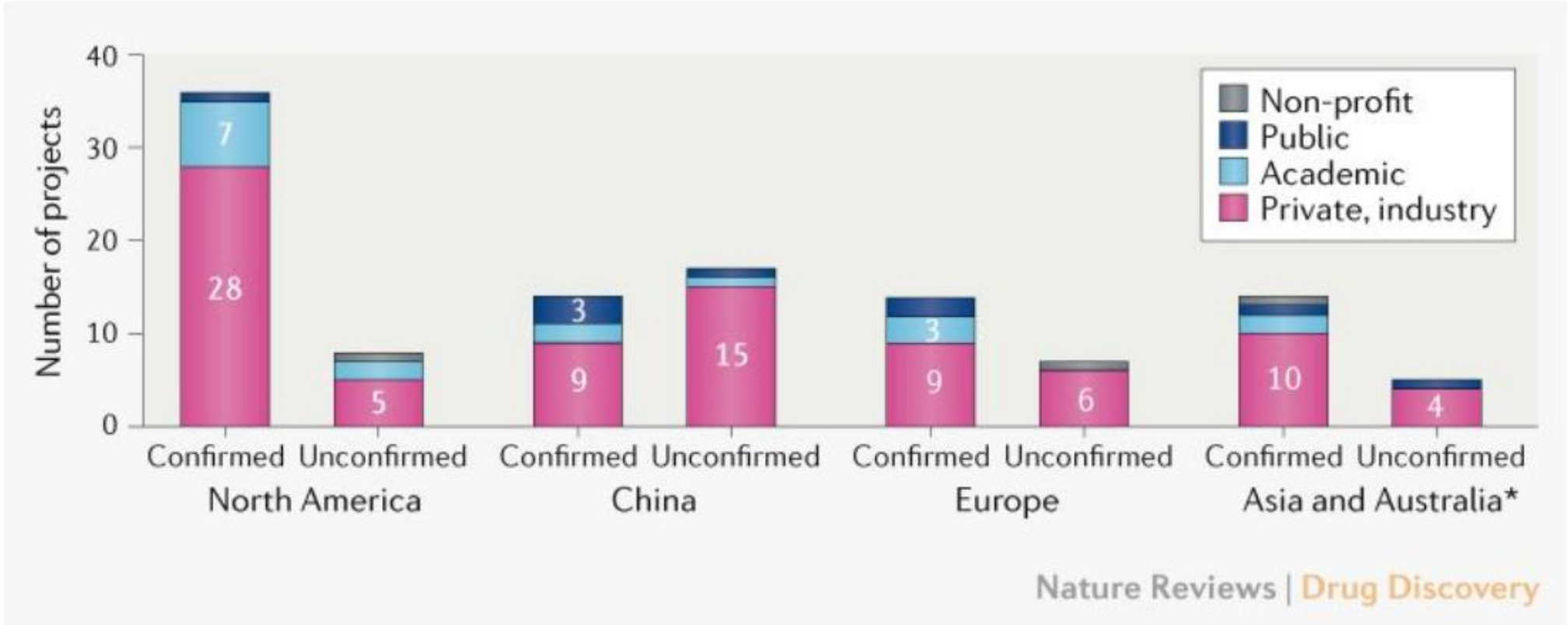


Fig. 2 | **Profile of COVID-19 vaccine developers by type and geographic location.** For partnerships, the location is that of the lead developer. *Excluding China.

Nature Reviews Drug Discovery

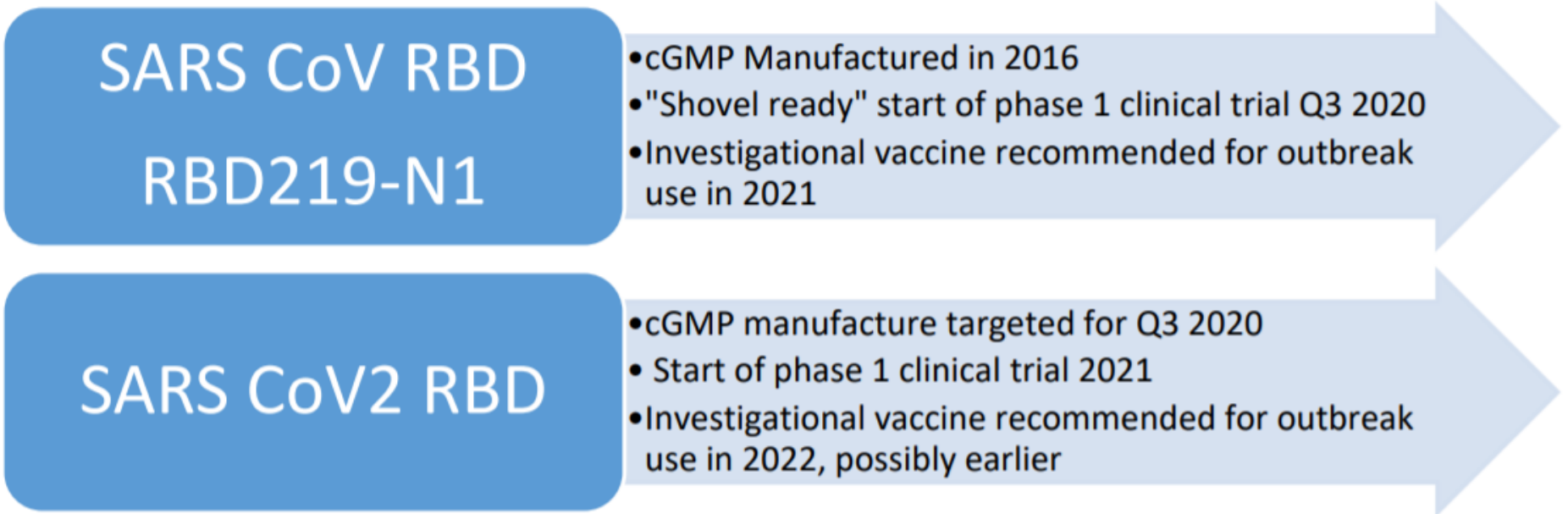
Table 3. Ongoing vaccine development for 2019-nCoV.

S/N	Company	Estimated Timeline	Technology	Stage/Funding	Reference
1	Moderna Therapeutics—US National Institute of Allergy and Infectious Diseases	3 months to early stage (phase 1) clinical trial in US (earliest); much longer for full testing and regulatory approval	Messenger RNA vaccine	Preclinical Awaiting preclinical tests and phase 1 study by NIAID, Funding by CEPI.	[62]
2	Inovio Pharmaceuticals	Human testing in the next few months	INO-4800-DNA based vaccine (DNA synthesized in lab, does not require actual virus sample)	Preclinical Funding by Coalition for Epidemic Preparedness Innovations (CEPI), up to $9 million	[62,63]
3	Novavax	3 months	Nanoparticle vaccine	Preclinical	[62]
4	University of Queensland	6 months	Rapid Response Technology, 'Molecular clamp' vaccine platform (gene added to viral proteins, misleads body to generate antibodies)	Preclinical Funding by Coalition for Epidemic Preparedness Innovations (CEPI)	[64,65]
5	Vir Biotechnology	Not available	Anti-coronavirus monoclonal antibodies. Additionally, using "whole-genome CRISPR-based screening capabilities to identify the host receptor for Wuhan coronavirus"	Preclinical	[66,67]
6	Chinese Centre for Disease Control and Prevention (CDC)	At least 1 month for development, 2–3 years before availability for use	Not available Inactivated virus vaccine (postulated, not verified)	Preclinical; virus successfully isolated, currently selecting strain	[68–71]
7	Shanghai East Hospital (Tongji University)—Stermirna Therapeutics	<40 days for manufacture of vaccine samples	mRNA technology	Preclinical	[72]
8	Johnson & Johnson	1 year to market	Adenovirus—vectored technology used for Ebola vaccine (and Zika and HIV vaccine candidates)	Preclinical	[73,74]
9	University of Hong Kong	Months for animal testing, At least 1 year for clinical trials on humans	Modified nasal spray influenza vaccine (with surface antigen of coronavirus) prevents both influenza and corona virus	Preclinical; vaccine developed	[70]

Table 3. *Cont.*

S/N	Company	Estimated Timeline	Technology	Stage/Funding	Reference
10	University of Saskatchewan (VIDO-InterVac)	Target for animal testing in 6–8 weeks, human trials in at least a year	Not available	Preclinical	[75]
11	GeoVax—BravoVax	Not available	Modified Vaccina Ankara—Virus Like Particles (MVA-VLP) vaccine platform	Preclinical	[76]
12	Clover Biopharmaceuticals	Not available	Highly purified recombinant 2019-nCoV S protein subunit-trimer vaccine (S-Trimer), produced using Trimer-Tag© technology	Preclinical	[77]
13	CureVac	Not available	mRNA technology	Preclinical	[78]
14	Texas Children's Hospital Center for Vaccine Development at Baylor College of Medicine	Not available	Not available	Not available	[79]
15	Codagenix	Not available	Not available	Not available	[79]

Estimated timelines of the SARS-CoV and SARS-CoV-2 RBDs as COVID-19 vaccines



Hotez, P.J.; Bottazzi, M.E. Developing a Low-Cost and Accessible COVID-19 Vaccine for Global Health. *Preprints* **2020**, 2020030464

A personal take on science and society

World view

Don't rush to deploy COVID-19 vaccines and drugs

By Shibo Jiang

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Safety testing must be paramount in measures to tackle the new coronavirus.

Around the world, I am seeing efforts to support 'quick-fix' programmes aimed at developing vaccines and therapeutics against COVID-19. Groups in the United States and China are already planning to test vaccines in healthy human volunteers. Make no mistake, it's essential that we work as hard and fast as possible to develop drugs and vaccines that are widely available across the world. But it

Phases de développement d'un vaccin

- Normalement : 15 et 20 ans
- formule possédant les prérequis chimiques et pharmaceutiques
- Etudes de :
  - **Immunogénicité chez l'animal,**
  - **toxicité du vaccin chez l'animal,**
  - **Toxicité du vaccin chez l'Homme, et enfin,**
  - **Efficacité à grande échelle**

Attention à l'effet des ADE

- *Antibody-dependant enhancement (ADE) :*
- facilitation de l'infection par des anticorps
- Phénomène constaté par Peter Hotez en 2003 sur certains animaux vaccinés
- vaccin contre le virus respiratoire syncytial développé par Pfizer 1960
- Vaccin contre la dengue de Sanofi
- Nécessité travailler sur lignées de souris modifiées génétiquement afin que leur réponse immunitaire soit identique à celle de l'humain

- Dans une réunion à huis clos, les responsables de l'Organisation mondiale de la santé (OMS) se sont mis d'accord pour autoriser les tests sur les humains avant que les résultats sur les animaux ne soient connus

Reuters

Global coalition to accelerate COVID-19 clinical research in resource-limited settings

www.thelancet.com **Vol 395 April 25, 2020**

Will vaccines reach low-income countries during a global pandemic?

*By **Michael Igoe** // 26 February 2020*

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Seth Berkley, CEO at Gavi. Photo by: CSIS / CC BY-NC-SA

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Bill & Melinda Gates Foundation, Wellcome, and Mastercard Launch Initiative to Speed Development and Access to Therapies for COVID-19

COVID-19 Therapeutics Accelerator will coordinate R&D efforts and remove barriers to drug development and scale-up to address the epidemic

SEATTLE, March 10, 2020 – The Bill & Melinda Gates Foundation, Wellcome, and Mastercard today committed up to $125 million in seed funding to speed-up the response to the COVID-19 epidemic by identifying, assessing, developing, and scaling-up treatments. The partners are committed to equitable access, including making products available and affordable in low-resource settings. The COVID-19 Therapeutics Accelerator will play a catalytic role by accelerating and evaluating new and repurposed drugs and biologics to treat patients with COVID-19 in the immediate term, and other viral pathogens in the longer-term. Currently there are no broad-spectrum antivirals or immunotherapies available for the fight against emerging pathogens, and none approved for use on COVID-19.

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